Lanoxin tablets: early stocks recalled

Burroughs Wellcome & Co announced on Tuesday that they had found that the Lanoxin 0·25mg tablets they were currently manufacturing had approximately double the effective potency of earlier batches. The company state: "Until very recently such differences were not detectable by assay procedures, but revised quality control systems have enabled us to manufacture Lanoxin tablets with a more predictable clinical response".

Pharmacists and doctors were warned of the finding and asked to return to wholesalers all stocks manufactured before May 1972 for replacement. The decision to recall was taken in consultation with the Committee on Safety of Medicines. Doctors were asked to review the dosages of all patients receiving the product.

A spokesman for the company explained to *C&D* that as from May the dissolution rate of Lanoxin tablets had been improved slightly and more effective monitoring of production, involving bioavailability tests, had been introduced.

It was not realised at first how much the small change in dissolution rate would affect availability within the patient. The company had acted promptly after encountering the new situation within the last few days.

Burroughs Wellcome now use a product known as Lanoxitest in healthy volunteers to give a measure of serum blood levels of digoxin. Preparations to be compared are given to the same volunteer to give a fair comparison. The test shows how much is being absorbed and over what period of time.

The spokesman said that the Association of the British Pharmaceutical Industry and wholesalers concerned had been informed of the company's proposed announcement before it took place.

A spokesman for Thomas Kerfoot & Co Ltd said they considered their digoxin product a consistent one. They had never had any comeback from the field.

A Boots Ltd spokesman said that the quality of Boots brand of digoxin tablets BP had not changed and patients stabilised on their tablets need not be concerned.

☐Mr C. A. Johnson, scientific director of the British Pharmacopoeia Commission, pointed out that present BP requirements for digoxin tablets are going to be augmented in the next BP. The monograph would include a test for uniformity of content for individual tablets.

Difficulties had arisen over the mixing of small quantities of digoxin with larger quantities of excipients prior to compression. Certain manufacturers were capable of producing tablets whose drug content varied from 60—130 per cent from tablet to tablet.

The Commission are taking account, in certain well defined instances, of difficulties which can arise over bioavailability. It is hoped to improve certain monographs as a consequence.

Koscot to be wound up

Koscot Interplanetary (UK) Ltd, the cosmetics company which operated a "pyramid selling" scheme (*C&D*, July 8, p 32) and a Swiss associate, Koscot AG, were compulsorily wound up in the High Court on Monday.

Announcing his decision, Mr Justice Megarry said: "The scheme reeks of cunning and dishonesty. It was a swindle, and a swindle of a far-reaching nature".

The petition for the companies' winding up had been made by the Department of Trade and Industry "in the public interest". The English company, of Ladmere Lane, Ruddington, Nottingham, was refused a stay of execution of the winding-up order pending appeal.

The judge said that plainly the moving spirit behind the whole scheme, as it was being developed in the United States and other countries, was a Mr Glenn Turner, with headquarters in Florida.

The judge said the petitions for winding-up had followed an examination of Koscot's affairs last year. The department also alleged that the public was induced to purchase the franchises by a series of reckless misrepresentations.

They submitted that before the petition was presented the sale of cosmetics formed only a minor part of the business—"so minor as to be almost trivial".

The judge commented, "The company contends that their market organisation had to be built up first. That may be so, but here the sales have been so small over so long a period, and the receipts from franchises so large, that the inference that the real business has been the sale of franchises is irresistible".

He added that he could not see the franchises conferring any tegal rights on the franchise holders. They were virtually worthless.

"As time passed, the scheme would have saturated the country with franchise holders, and the prospects for each one receiving any real rewards would have become less and less."

C & D Award at the Conference

Ninety-two science papers and communications will be presented at the British Pharmaceutical Conference at Keele, September 11-15.

Chemist & Druggist is awarding a silver medal and £25 to the author of 30 years or younger who gives the best presentation of a paper or communication at the conference. The award will be made on the recommendation of the Conference Science Committee.

It has been announced that Lord Rosenheim, chairman of the Medicines Commission, and Professor A. R. Gemmell, Keele University will be the principal speakers at the Banquet.

Science group election

Four members of the British Pharmaceutical Conference Science Group Science Committee retire at the next business meeting of the group to be held at Keele on September 12 at 4.45 pm. They are: J. E. Carless, P. H. Elworthy, J. W. Hadgraft and W. Gwynne Thomas. Nominations for membership of the committee may be made from among members of the Science Group, preferably before the meeting in writing.

Nominations require a proposer and seconder and should be sent to the secretary, Conference Science Committee, 17 Bloomsbury Square, London WC1A 2NN. At the meeting the Science Committee will recommend changes in this procedure for 1973. The proposal is that nominations be made in writing by a proposer and seconder not less than one month before the business meeting each year. Other members of the Committee are: W. C. Bowman, M. R. W. Brown, D. J. G. Davies, J. R. Fowler (secretary) Betty P. Jackson, C. A. Johnson, the director of the Department of Pharmaceutical Sciences (S. C. Jolly), K. A. Lees, and B. A. Whittle.

The Chemist & Druggist *Research medal*

Beecham get order against cut-price firm

Mr Roy Sylvester Smethurst, trading as Cosmeda Chemists, 133, High Street, Balham, was ordered by the High Court last week not to retail Beecham Group proprietary medicines, sold subject to a price condition, below the price in the Group's current list.

Mr Gavin Lightman, for Beecham, told Mr Justice Megarry that last January Mr Smethurst was found to be selling Beecham's medicines below the fixed prices. The area sales manager was instructed to serve notice on him to comply with the price condition.

In June Mr Smethurst was still cutting the price and a test purchase of Dinneford's Gripe mixture was made. The price charged was £0.17½ whereas the fixed retail price was £0.20.

The judge said that Mr Smethurst, who did not contest the action, would have a week from the day the court order was served on him to make any necessary alterations to his price tickets on Beecham's medicines.

☐ Quality Fare Ltd, whose registered office is at Station Approach, South Ruislip, Middlesex, submitted in the High Court last week to a permanent order restraining them from selling Beecham's powders, or Setlers, or any other Beecham's proprietary medicines at prices lower than those fixed in Beecham's current price list.

By agreement, the company are to pay the costs of Beecham Group Ltd, who brought the proceedings before Mr Justice Goulding.

Drug patent renewals

Mr L. Pavitt asked the Secretary of State for Trade and Industry, if he would refuse to extend the patent coverage on any drug used extensively by the National Health Service when it reached its due expiry date.

Mr Michael Noble, Minister for Trade, replied: "Extension of the term of a patent is not a matter for the Secretary of State. It is decided by the High Court except in the now very rare case when application for extension is made to the Comptroller General of Patents on the ground of war loss".

ABPI sponsors teacher's guide to pharmacy

The Story of Medicines, a new publication for schools, sponsored by the Association of the British Pharmaceutical Industry, is the second in a series of educational desk-top "flow charts" being published by Tony Davies Associates Ltd. The chart and teacher's guide book running to 25,000 words were written by the late Mr Owen H. Waller, FPS former editor of *Chemist & Druggist,* It was Mr Waller's last major commission before he died in February.

The commentary on the chart has been aimed at children aged between seven and 14. The story is told in greater detail in the guide book for the teacher. The full-colour illustrations are based on authentic sources and the complete publication has had the approval of the Pharmaceutical Society of Great Britain.

The charts are being sold to schools by the publisher at a special price agreed with the sponsor, in storage wallets each containing ten colour charts plus one teacher's guide, at £0.75 plus postage. Others interested may obtain sets consisting of one chart and one guide for £0.25 per set, post free from the ABPI, 162 Regent Street, London W1R 6DD.

Equivalency discussed by BMA

The Government are urged to ensure that the formulation of all drugs available in this country conform to a specified standard of therapeutic efficacy in a British Medical Association resolution passed at its representatives meeting recently.

Proposing the resolution Dr G. A. Griffin of Bromley said that a drug company film suggested that generic equivalents were not in fact equivalents. Their formulations varied. Why was this? The BP specifications were not tight enough. There were variations of 10-15 per cent.

Commenting Sir Ronald Tunbridge chairman of the BMA's board of science pointed out that the Medicines Act covered those contingencies. The trouble was that with the pressure of new drugs, it had not been possible through the time factor to work through all those on the market, but this matter was very much before those serving on different aspects of the Medicines Commission.

Another motion which was carried stated: "That the Government be asked to oblige firms to have a standardised code for identification on their products."

The meeting expressed its gratitude to the panel on pharmaceutical products for an outstandingly useful and practical report (*C&D,* May 20, p 711) and Sir Ronald Tunbridge referred to the same report. He said it was pleasing that the members of the pharmaceutical profession, the industry and the board could agree to practical suggestions to deal with the problem of safety of drugs.

Most coupons delivered direct

Some 55 per cent of all coupons redeemed in the UK in 1971 had been distributed to housewives by direct mail or "door to door", according to estimates in a recent survey undertaken by Nielsen Clearing House, the coupon clearing division of A. C. Nielsen Co Ltd.

"In" or "on-pack" coupons accounted for a further 33 per cent of redemptions, and the remaining 12 per cent had appeared in newspapers and magazines. Mr David Charlton-Jones. manager of the division, believes that these figures could change markedly in the next few years, as the opportunities to use regional editions of magazines and newspapers increase.

The survey also includes estimates for US coupon redemptions. which show how the size of the country and higher basic wage scales keep the proportion of direct mail and door to door coupon redemptions down to 14 per cent. Newspapers and magazines dominate redemptions with 60 per cent of the total, reflecting the comparative ease of running strong regionalised press promotions in the US and. of course. the high cost of door to door distribution. "In" or "on-pack" accounted for 26 per cent.

According to Mr Charlton-Jones: "Our survey also showed that coupons, at last, are beginning to follow the two sizes most easily handled by retailers—that of a pound note, and the IBM card size."

Change of heart on centres

The idea that clinical tutors are not willing to collaborate with disciplines other than medicine in the educational activities of postgraduate centres is referred to as a misconception in a letter published recently in *British Medical Journal*

The correspondents, the secretary and chairman of the National Association of Clinical Tutors, are concerned that any new type of hospital education centre should "remain in the hands of the doctors".

They refer to a proposed conference between all those concerned with the planning and work of postgraduate centres, which is being arranged by the Council for Postgraduate Medical Education.

Earlier they had announced that the National Association was unanimous in its view that adequate accommodation had to be available primarily for medical staff and under local medical control (*C&D,* June 10, pp 793 and 805).

Importers seek higher prices

Private drug importers in Sri Lanka are seeking higher prices for imported drugs. They want an increase of at least to the extent to which the value of the rupee has fallen by almost 10 per cent since it was allowed to float in the international market from November 1971.

In addition, they say that as a result of the change in the value of the rupee they are called upon to pay higher duties as duties are assessed according to the current value of the rupee and not according to the value of the rupee at the time the goods were ordered.

This year drug importers will be allocated a lesser quota for imports than earlier as the State Pharmaceutical Corporation has taken over the import of 38 drugs from this month.

The Corporation, which took over monopoly rights for the import of insulin from January, has priced it higher than when it was imported by the private trade.

'Here at last is the White Paper'

"Reform of the National Health Service has been under discussion for 10 years, here at last is the White Paper as a prelude to legislation." So said Sir Keith Joseph, Secretary of State for Social Services, when presenting his paper on Tuesday.

Sir Keith agreed that it bore a close resemblance to the earlier Consultative Document but said that there was an increased emphasis on professional advisory machinery.

The White Paper states that the Act will include provision for strong professional advisory machinery to be built into the new structure at every level.

Area Health Authorities under the Act will have a statutory obligation to determine the health needs of the communities they oversee. In terms of the allocation of resources Sir Keith said that it was a case of the dramatic winning over the commonplace at present. Unspectacular health requirements were being neglected and the new legislation would aim to change this.

Sir Keith said he envisaged "patient teams" serving "patient groups".

See p 198.

ABPI co-operate with Hungary for seminar

The Hungarian Chamber of Commerce, in co-operation with the London Chamber and the Federation of Technical and Scientific Societies of Hungary, and in association with the Confederation of British Industry, is organising a series of lectures in November on recent achievements in industry and technology, with the aim of exploring possibilities for industrial co-operation with British companies.

A two-day seminar will be held in the forum series of the London Chamber of Commerce and Industry.

The second day's programme, organised in co-operation with the Association of the British Pharmaceutical Industry, will be devoted to pharmaceuticals. The lecturers will include Mr Gy. Horváth, vice-president of the Union of the Hungarian Pharmaceutical industries; Mr L. Kisfaludy, head of the Richter Research Laboratory; Professor J. Knoll, from the Semmelweiss University of Medicine; Dr Z. Tuba, from the Richter Research Laboratory and Dr J. Szejtli, head of the Chinoin Biochemical Research Laboratory.

Queen's Awards to Industry 1973 arrangements

The Office of The Queen's Award to Industry has announced that application forms and guidance notes for the 1973 Awards are now available. The award can be applied for by any United Kingdom based organisation producing goods or providing services who seek recognition for outstanding achievement in increasing the exports of this country or in the advancement of product or process technology. The last date for applications is October 31, 1972

Inquiries about eligibility for the award and application forms should be made to:—The Secretary, Office of The Queen's Award to Industry, 1 Victoria Street, London SW1H 0ET. Telephone No: 01-222 2277

Deaths from paraquat

There were three recorded deaths in England and Wales during 1970 from paraquat Mr M. Alison told the House of Commons last week.

Most of the accidents occurred because the chemical had not been stored in its original container. The Government did not intend to impose a ban upon the sale of paraquat because the Advisory Committee on Pesticides and Other Toxic Chemicals has advised them that if the precautions which they have recommended (including that on storage) and which appear prominently on the label of every original container are followed there should be no danger to anyone.

Information was not available centrally about cases successfully treated.

The local committee at Chester discussing luncheon arrangements for the Conference's all-day excursion. Seated are Mr A. Evans, visual aids officer, and Mr E. Burrows, treasurer. Standing (left to right) Miss J. Platt, ladies' representative; Mr N. Durber, transport; Mr C. Turner, chairman; Mr H. Morrell, transport officer; Mr A. M. Elliott, assistant manager of the Grosvenor Hotel; Mr P. E. Taylor, secretary, and Mr M. Edwards, assistant Secretary.

The committee has been progressively covering the ground of all the excursions and events. Some members were seen testing the temperature of the swimming pool in Trentham gardens recently

M & S sell Sanpro

Marks & Spencer extended their range of toiletries this week and entered the feminine hygiene market with the introduction of sanitary towels and tampons.

Both products are being distributed through 24 selected branches spread over the country, including London's two Oxford Street stores.

The tampons, which include an insertion tube are packed in 20's and are priced at £0·25 for the regular size and £0·28 for the super. Also competitively priced are the looped sanitary towels at £0·18 for size 1 and £0·21 for size2. These are packed in 15's instead of the traditional dozen, as this number is believed by M & S to answer "the needs of the average user for one period". A cosmetic approach to packaging has been adopted, both items including a colourful floral design.

No ban on opiates

Mr Laurie Pavitt asked the Secretary of State for Social Services, if he would establish a working party to examine the findings of the World Health Organisation technical report series number 495, with a view to securing the substitution of other compounds to replace opium, morphine and codeine in National Health Service prescribing.

Sir Keith Joseph, Secretary of State, replied "No". The report showed that the available synthetic alternatives had not been demonstrated to be clearly superior to the opiates in some conditions, and he thought it right that doctors should be free to decide which drug to use in the treatment of individual patients.

Tinned baby foods

A Chigwell, Essex Councillor has suggested that all tinned baby foods should be cleared from shops and replaced with bottled food. The council was studying the recent Government report (*C&D*, July 8, p 33) which said food can be contaminated by lead from the solder used in tin cans and babies were more prone to lead poisoning than adults. It was decided to refer the matter back to the Public Health Committee for further consideration by the Medical Officer of Health.

Pharmaceutical imports-exports

There were no separate figures for the value of imports and exports of "patented" pharmaceuticals nor for royalty transactions on drug patents, Mr Michael Noble, Minister of Trade told the Commons in reply to a question. Taking pharmaceuticals as a whole, during 1971 exports were valued at £168.4 m. and imports, he said, £37.6 m. Both the export figure and the balance of payments surplus were new records for the pharmaceutical industry.

Customs and Excise launch VAT campaign

Customs and Excise are launching their largest-ever trader information and publicity campaign in preparation for the introduction on April 1, 1972 of VAT.

First phase of the £1m campaign began last Friday with the appearance in 25,000 Crown and sub-post offices of copies of a leaflet entitled *VAT in Small Shops and Businesses*.

This early phase of the campaign has two main messages the Customs say—to inform the business community of the Department's plans for the introduction of the tax, including registration dates and the distribution of official literature; and to encourage retailers and small businessmen to get the leaflet from post offices.

The eight-page leaflet is intended as an introduction to VAT for small traders. It gives a brief description of what the new tax is, how it works and answers eleven basic questions on such matters as registration and accounting for VAT.

Mid-August will see the postal distribution to some 1·4 m traders of two 80-page booklets, *VAT General Guide* and *Scope and Coverage*, and other information, including a registration form and a reply-paid card to enable them to order extra copies and more specialised literature.

The main phase of the campaign (October-January) will concentrate on registration, but traders will also be advised of the need to prepare for VAT, particularly with regard to accounting. Posters on registration will also be displayed in post offices and many banks.

The BBC have made a 35-minute colour film, "VAT Special", with the small trader especially in mind. It is scheduled to be shown at noon on Sunday, September 24. Arrangements have been made for trade groups and business organisations to obtain 16mm copies of the film on free loan from the Central Film Library from September 25.

In the Autumn display units giving basic information about VAT will be available on free loan from Customs and Excise headquarters for conferences, seminars and other events sponsored by trade organisations and business groups.

Some 1·5m traders are expected to register for VAT. Registration will be staggered alphabetically so that the operation can proceed smoothly between October and January. Businesses with names beginning A-C will be asked to register during October; D-J during November; K-Q during December, and R-Z during January 1973. Registration forms will be issued with the *General Guide*.

The Department have agreed to provide speakers for more than 750 meetings in the coming months.

Ulster Chemists' Conference arrangements

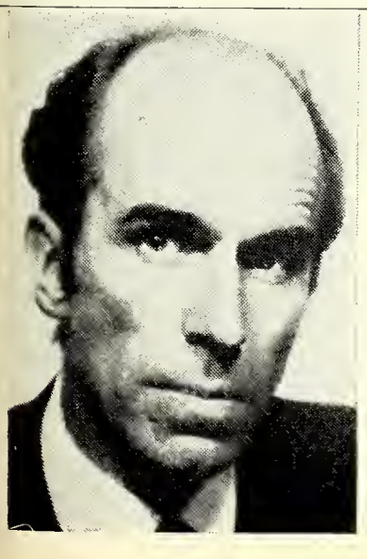
Despite the disturbed state of the province, the UCA Executive Committee has decided that the annual conference should be held as usual in view of the important imminent changes affecting pharmacists including VAT and entry into the Common Market. The Conference is to be held at the Slieve Donard Hotel, Newcastle, Co Down and the programme is as follows:—

Friday September 29.
9.0 pm Social get-together.
11.30 pm Toast to the Conference by the president.

Saturday September 30.
10.30 am "VAT without Tears" by T P Astill, Esq. B Pharm, MPS, Personal assistant to the director of NPU Group.
2.0 pm Excursion to Silent Valley.
4.0 pm Afternoon tea at Kilmorey Arms Hotel, Kilkeel.
8.0 pm Conference dinner.
9.30 pm ,, dance.

Sunday October 1.
2.30 pm "British Pharmacy and the Common Market" Allen Aldington, BOE, FPS, Member of N.P.U. Executive Committee).
3.45 pm "The N.H.S. Contract and Remuneration" by M. M. McNeill, FPS, (Secretary Pharmaceutical General Council Scotland).
Afternoon Ladies' excursion, tea at Enniskeen Hotel Newcastle, Co Down.
7.0 pm Farewell dinner.
Parties for swimming, riding, golf and fishing arranged as required.

The inclusive hotel charge for resident members for the full Conference is £11 per person plus 10 per cent service charge, children under 12 one-third reduction. Charge to visiting members for the dinner and dance £3 per person, Conference residents £1 per person.



Basle to Leeds

Mr Robert Foster Weir, BSc, MPS, recently appointed deputy managing director of Reynolds & Branson Ltd, Leeds (subsidiary of Barclay & Sons Ltd), will have responsibilities for pharmaceutical facilities at Rawdon, Leeds. Prior to this appointment Mr Weir was vice-director and head of pharmacy research and development of Sandoz Ltd, Basle. He joined Sandoz in 1960 and previous to his Basle appointment was manager of the pharmaceutical factory of Sandoz at Horsforth, Leeds

UCA Executive Committee election

The following members are due to retire from the Executive Committee at the annual general meeting— J. Doyle, T. M. Glass, I. D. McKee, W. J. Moffett, A. Moore, J. Paul and R. F. S. Thornton. Mr J. C. McCrea has indicated that he does not wish to stand for re-election, but the other members are eligible for nomination, and nominations should be lodged with the secretary not later than midday September 20. No special form of nomination paper has been declared necessary.

Damage reminder

The Ulster Chemists' Association Committee remind members that if they suffer bomb damage during the current troubles they must notify their solicitor immediately; he has ten days to put in a preliminary claim for compensation.

Herbie Gamble memorial fund

The local Pharmaceutical Committee, Northern Ireland has launched a fund in the memory of the late Mr H. W. Gamble, OBE. It has been agreed with the Council of the Pharmaceutical Society of Northern Ireland that a room in the Society's house at 73 University Steret, Belfast is to be known as "The H. W. Gamble Room" to be used for Members of the LPC and its successor under the restructuring of the General Health Services, the Pharmaceutical Contractors Committee. The room is to be refurnished and redecorated and a commemorative plaque is to be placed in the lecture hall. The local Pharmaceutical Committee have invited contractors to subscribe to the H. W. Gamble memorial fund; cheques should be sent to the treasurer of the local Pharmaceutical Committee, 73 University Street, Belfast 7.

Local Pharmaceutical Committee

In accordance with the rules of the local Pharmaceutical Committee half of the committee members representing each area are due to retire on September 30. Currently serving members eligible for re-election are:—
Belfast: Messrs. R. N. M. Clarke, T. W. Currie, J. W. A. Shinner and J. G. Stinson.
Londonderry: B. J. McCloskey.
Co Antrim: H. G. Campbell.
Co Down: J. C. Gouk.
Co Londonderry: T. M. Glass.
Co Fermanagh: W. J. Mullen.
Co Tyrone: T. G. Rutledge.
New nominations for committee membership should be lodged with the Secretary not later than midday September 1.

Illegal drugs

The number of regular illegal drug users has trebled in five years, says the *Police Review*.

Pot smoking has increased alarmingly with youngsters refusing to believe a "non-addictive drug" is dangerous.

New "packs" for making LSD are flooding the black market and are responsible for hundreds of new users.

COMPANY NEWS

Beecham's statement on research

Addressing shareholders of Beecham Group Ltd last week, the chairman, Sir Ronald Edwards, said that "the international competition" in pharmaceuticals had "showed a sort of stunned relief at the monopolies thumbs down" for the Beecham-Glaxo merger.

He said: "We shall never know whether the Commission's judgment was right, because we shall never know what Beecham and Glaxo together would have achived. There is nothing in the Commission's report which has altered my conviction that such a merger would have strengthened the world-wide position of the British-owned industry".

'Significant research'

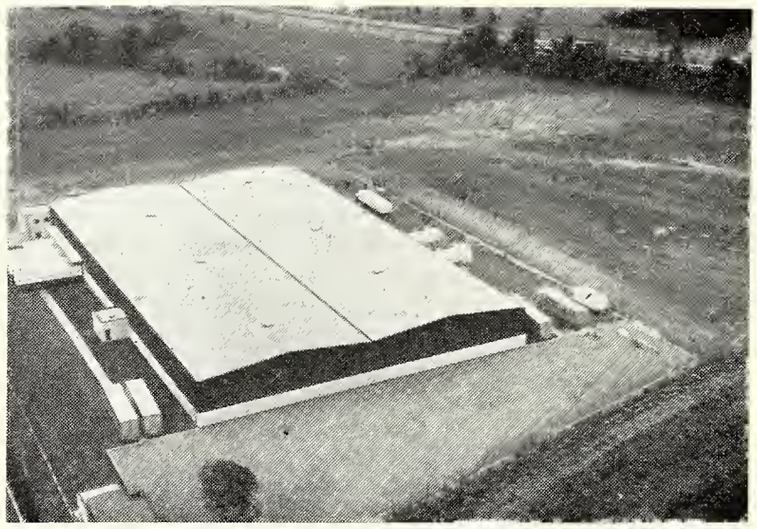
Dealing with that part of the report which said: "Beecham's research interests are relatively narrow . . ." Sir Ronald said the Group had "significant research projects in several therapeutic areas which together account for more than half of the total pharmaceutical market, and other projects which cover a further sizeable segment of the market". The larger part of the budget—in fact, some 70 per cent—was outside the main area of their business, namely antibacterials.

The board, he said, had never lost sight of the importance or the potential in the business from which the resources for our pharmaceuticals sprang—consumer products. "It is our policy to continue in this way."

On the overseas side Sir Ronald reported that they were now getting on top of the problems at the New Jersey factory, and that the second half-year should see the benefits of an efficient factory coupled to a re-trained and re-deployed sales force. Beecham Inc's overseas business was also making good progress.

In the United Kingdom the company's toiletries were going through a successful period.

At the moment their biggest European sales effort in pharmaceuticals was in France, and development expenditure there was currently "very high".



Johnson & Johnson's Patchway distribution centre strategically sited by the M5 motorway seen at top of picture (story below)

Higher dividend from Macarthys

Group profit, before tax, of Macarthys Pharmaceuticals Ltd expanded from £695,849 to a record £1,087,089, for the year ended April 30. The dividend is effectively raised from 11 to 18½ per cent with a final of 14 per cent.

The directors also report that present indications during the current year are "encouraging in all activities".

Taxation takes £444,246 (£282,351) leaving a net profit of £642,843 (£413,498).

Savory & Moore and Macarthys Laboratories recorded substantial improvements in profit: together with further advances in the wholesale field they have contributed significantly towards "our most successful year to date" say the directors.

J & J open new central depot

Johnson & Johnson Ltd, have opened a new distribution centre sited at Patchway on the M4-M5 interchange. A review of the total distribution system has led the company to close a number of smaller warehouses. A fleet of 40 articulated vehicles transport products from the company's three factories to Patchway where they are stored and distributed.

Orders for some customers are fulfilled directly from the central store which is directly linked to over 750 miles of motorway. Certain locations were found to be better servieed by local deliveries. In those areas regional warehouses have been retained, and they will be served by Patchway. The new distribution network has enabled the average time from receipt of an order to delivery to be reduced to five days.

Working a shift system round the clock, orders will soon be received via a telex link from the customer service centre at Slough.

Polaroid's plans for new home

Polaroid (U.K.) Ltd will be moving their headquarters in the latter part of 1973 to a new purpose-built office and warehouse complex totalling some 62,000 sq ft on a site currently being developed in Ashley Road, St Albans, Herts.

The company has exchanged contracts for the construction of the projected building at an estimated cost of more than £800,000.

Polaroid currently occupy two floors of Rosanne House in Welwyn Garden City to house the head offices, marketing teams and accounting staffs while the company's distribution centre is located at Welham Green, near Hatfield. Initially, the new location will house about 100 people, bringing together on one site the largest part of Polaroid's distribution organisation. (Polaroid UK's manufacturing division has over 300 employees based at the Vale of Leven factory in Scotland.)

Laporte sound a cheerful note

Mr Aubrey Jones, chairman, told the annual meeting of Laporte Industries (Holdings) Ltd last week that unless something unexpected arose he believed that the worst of the difficulties had been overcome and that for 1972 the board would recommend an increased distribution of profits to shareholders.

"Much, however, remains to be done to restore to the company an acceptable rate of profitability."

Leiner forms European link

Mme Sterling and Mr J Kinet have been appointed directors in Paris and Brussels respectively of P. Leiner & Sons, SA, a new European company formed by P. Leiner & Sons Ltd, Treforest, to increase their gelatin sales in the EEC countries.

Mme Sterling was previously sales director of Compagnie Gelatine Francaise and Mr Kinet was formerly managing director of Unigel SA and before that sales director of Cogelos, Belgium. The directors of P. Leiner & Sons will also be on the board of the new company.

Statement from Syntex

A former medical representative of Syntex Pharmaceuticals Ltd, Maidenhead, Berks, instituted proceedings through the Industrial Relations Court relating to his dismissal, proceedings which were opposed by Syntex. Much of Mr Baldwin's case was presented at the first day's hearing but before the resumed hearing took place Mr Baldwin withdrew his application.

Syntex state that no financial settlement of any kind was made by them.

In brief

National Cash Register Co reports net earnings for the second quarter were $2·79m on revenues of $384·49m. This compares with $7·01m on revenues of $367·41m in the second quarter of last year. A net loss of $6·81m in the first quarter however, means that for the first half of 1972 there is a net loss of $4·01m on revenues of $711·29m.

Bayer Aktiengesellschaft (Bayer AG) is the new name for Farbenfabriken Bayer AG. The company say that the previous name, chosen for its links with the original founder company, was no longer in line with their diverse fields of activity.

Trinity Pharmacy and the head office of **Howe & Hammond Ltd** have moved to 92 South Street, Bishop's Stortford, Herts.

R. Weston (Chemists) Ltd have acquired the pharmacy of F. V. Brown & Co, 41 High Street, Buxton, as from August 1.

PEOPLE

Mr Douglas Stafford, FPS, executive vice-chairman, Beecham Group Ltd, retired at the end of July. The news that Mr Stafford was about to retire was given to shareholders of Beecham at their annual meeting last week when the chairman, Sir Ronald Edwards said that he had known of Mr Stafford's wish to retire before the normal retirement age for some time because he had recently been through a period of considerable pain with a leg condition which was now responding to treatment. During the 36 years Mr Stafford had been with Beecham almost all the full-time directors had at one time worked for him.

Mr Stafford served his apprenticeship with Boots Ltd, qualifying in 1931. He was manager of Endocrines-Spicer when that company was acquired by Beecham. He was president of the Association of the British Pharmaceutical Industry 1965-66.

Graham Bool (24) manager of the Agfa-Gevaert showroom in Piccadilly, London has been chosen to represent Great Britain in this year's Olympic Games for the disabled in Heidelberg, August 1-11.

Mr. Bool, disabled by polio in 1949, started playing wheelchair basketball five years ago, just before the last games held in Israel (not Mexico because of the acclimatisation problems). For the last three years he has been training very hard under the watchful eye of the England coach, and has shown great determination and courage. Mr Bool will be taking part in the 100 metres sprint, the slalom and wheelchair basketball.

The amount of effort involved is tremendous when you realise that an Olympic runner covers 100 metres in 9.8 secs and a disabled sprinter covers the same distance in just 21.2 secs.

Deaths

Bradbury: Recently Mr G. D. Bradbury who was London area representative of Li-Lo Ltd for over 25 years.

Rae: On July 23, Mr Alec Rae, MPS, Whinmead, Prestwood, Great Missenden, Bucks. Mr Rae qualified in 1925.

Appointments

Retail Alliance: Mr John Hussey has been appointed secretary of the Retail Alliance on Mr J. Ramage's retirement.

Dorothy Gray have appointed Mr Ken Lofts their marketing manager. Mr Lofts was overseas marketing manager for the company with whom he has been for five years.

Schering Corporation, New Jersey: Mr W. H. Conzen has been elected chairman of the board; Dr Donald R. Longman, president and chief executive, and Francis J. Gleason, executive vice president and chief operating officer.

Vestric Ltd have appointed Mr R. W. Perry area sales manager covering the central midlands sales area. Mr A. J. Brewster has taken up a new position as chemist representative at Ruislip branch; and Mr A. F. MacMullan, chemist representative at Gibbs, Bristol branch. In branch operations Mr P. F. Jerrome, has been appointed assistant branch manager at Sandwich.

NEWS IN BRIEF

☐ The International Chemical and Petroleum Engineering Exhibition is to be held at Olympia, London, September 18-22.

☐ The National Wages Board has rejected an application for four weeks annual holiday for co-operative pharmacy shop managers and manageresses.

☐ The Poisons List Order (Northern Ireland 1972 SRO 1972 : 142) and the Poisons Regulations (Northern Ireland) 1972 (SRO 1972 : 144) became operative July 15. The order and regulations are available from HM Stationery Office, Belfast price £0·10½ and £0·37 respectively.

Topical reflections by Xrayser

Martindale

The arrival of the anticipated "Martindale" has meant a re-arrangement of the bookshelf in the pharmacy. The twenty-fifth edition fitted neatly into a pigeon-hole, whereas the twenty-sixth has filled out a bit and has to be accommodated elsewhere. But I have done that more willingly for the Extra Pharmacopoeia than I have done for redesigned packs of some of the products in daily use in dispensing, particularly those described as "unit" packs, which, we were assured, would take up less space than the bulk pack.

I am not sure whether the BBC has ever invited a pharmacist to take part in its programme of desert-island discs, but I imagine that the pharmaceutical castaway would opt for a copy of Martindale to help him in his exile. He could keep himself up to date with the latest releases of the drug manufacturers—for a week or two at least—and if he felt a trifle sentimental he could compose a lyric from such euphonious items as oil of Betula lenta, or that obtained from Melaleuca leucodendron. And the classicists of old would not have rejected Oleum Melissa out of hand, nor, one fancies, Pino Pumilionis, while, if lieder were his forte, Der Muskatnuss might inspire him to write something for Fischer-Dieskau.

But there are other things, such as 150 pages on penicillins and other antibiotics, and it seems no time since the whole of the information could be crammed into a page and a half. A new one—to me—came my way the other day in the shape of a product containing tetracycline and proteolytic enzymes, and, always avid for information, I read the accompanying leaflet. The contra-indications, it stated, were in patients with known sensitivities to enzymes or tetracyclines, and that seems eminently sound. I have known people with known sensitivities to lobsters or strawberries, and such peculiarities must be recognised and evasive action taken. But I feel sure that a perusal of the toxic effects of many of the medicines of today would bring home to the castaway that his chances of survival had not been lessened by his nautical misfortune.

Dental health

I had not realised that there were so many different toothpastes on the market until your special issue dealing with the subject appeared last week. Tubes of toothpaste were a rarity in my early days, when the principal output was tooth powders. Many dentists had their own particular formula, and the patient could generally be relied upon to provide apprentice work with a large mortar and pestle and a fine sieve. A so-called "antiseptic" powder of the period might contain castile soap, orris root of the Florentine variety, chalk and a trace of carbolic acid. Others might be flavoured with otto of rose—kept in the safe, the bottle itself encased in a metal container as though it were a radio-isotope. The oil was measured under the eagle eye of the Governor himself, and it shared the safe with musk and a little money.

Antimonial tooth powder

Other powders 70 years ago contained carbonate of magnesia, long before the makers of a popular magnesia preparation turned their thoughts to dental care, and such odd items as rhatany and myrrh appeared in other formulations. One such even contained a little antimony, and all were presented in elegant packs.

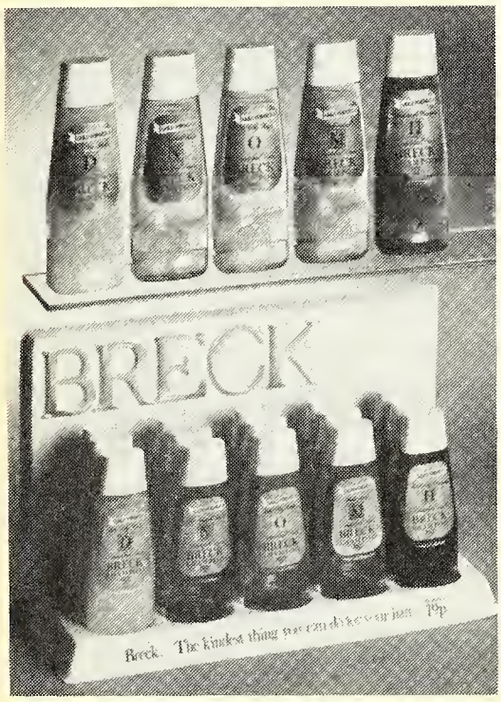
TRADE NEWS

Gold formula shampoos

The Breck range of shampoos has been relaunched under the banner of "Gold Formula" with a formulation giving high lather, and "new gentle kindness".

The collection comprises Egg protein for dry hair, Conditioning shampoo for normal hair, Lemon for oily hair, Medicated with fentichlor to help control dandruff, and Herb shampoo. All are available from Shulton (Great Britain) Ltd, Trevor House, 100 Brompton Road, London SW3, in 70cc (£0·19) and 115cc (£0·29) PVC bottles and sachets (£0·05) with the exception of the herb preparation which is not obtainable in sachets until early September.

The bottles are tapered to allow ease of handling from self-service displays and have screw tops, similar in shape to the previous design.



Roter tablets in 20s

FAIR Laboratories Ltd, 179 Heath Road, Twickenham, Middlesex, are introducing Roter tablets in 20-tablet packs (£0·29) and as an initial bonus are offering 20 packs invoiced as 18 during the introductory month of September. Counter display packs will be available only from wholesalers from September 1 onwards, but retailers are asked to place their orders now to ensure they receive required supplies.

Reformulated baby cream

Johnson & Johnson Ltd, Slough, Bucks, have introduced a reformulated version of their baby cream in 45g (£0·23) and 85g (£0·39) sizes in new packaging. This preparation, which follows two and a half years of research and development, is said to produce a permeable but moisture resistant screen, enabling the skin to function properly and is neutral so as not to affect the natural acidity of the skin.

This is not the case with most water in oil creams which often rely upon alkaline soaps to stabilise the emulsion, say the company, and tend to upset the skin's balance, laying it open to attack by alkaline decomposition on the nappy.

☐ The company have also revamped their cotton buds and baby shampoo, also in redesigned packaging. The buds incorporate a blue fluted stem with softened heads and come in three sizes, medium (£0·09), large (£0·21) and economy (£0·29), while the shampoo is said to have a richer, thicker texture and a new delicate perfume "more suited to adult usage". The shampoo is available in 85cc bottles (£0·23) and a sachet (£0·06).

ICI distribution

Imperial Chemical Industries Ltd, pharmaceutical division, Alderley Park, Macclesfield, Cheshire, have asked us to point out that their Savlon babycare products are on sale only from chemists and pharmacy departments in department stores.

Bacterial antigen therapy

Pharmacists in general practice are invited to write to Lantigen (England) Ltd, Bagshot, Surrey concerning special display and trade terms available in respect of Lantigen B.

The company state that the efficiency of the preparation has been confirmed in clinical trials and it is being increasingly recommended by doctors.

Atromid production problem

Imperial Chemical Industries Ltd, Alderley House, Alderley Park, Macclesfield, Cheshire SK10 4TF, say that owing to production difficulties of the 500s pack of Atromid 500ml it will be necessary from about August 14 to despatch in multiples of 250 for orders received for the 500s pack. This state of affairs is likely to remain for approximately two months, after which they they expect production to return to normal.

Germoloids tissues

Beecham Products (UK), Beecham House, Great West Road, Brentford, Middlesex report an exceptionally good trade response to their Germoloids moist toilet tissue (£0·20).

These tissues, individually wrapped in foil sachets, are aimed primarily at those suffering from piles, pruritus and similar conditions as well as "the hygiene conscious". The product, packed in cartons of 10, is being advertised in national daily and Sunday papers as well as women's weekly magazines.

Bonus offers

Weddel Pharmaceuticals Ltd, 14 West Smithfield, London EC1A 9HY. Derl. 48 invoiced as 40 (until October 31).

Robinson & Sons Ltd, Wheat Bridge Mills, Chesterfield. Poppon and de luxe baby pants. Through representatives only. Thirteen invoiced as 12, with a choice of style on a mixed order of ½doz of each.

NEW PRODUCTS AND PACKS

Over the counter medicinals

Abdine powder packs

Abdine Ltd, acquired January last by Mr Lawrence Sammerhoff and transferred to Glasgow, have introduced newly designed packs for Abdine powders.

Folded in white and blue papers, the ordinary strength powders are banded by a yellow wrapper printed in blue and the double strength with a white wrapper printed in blue (Abdine Ltd, 110 Commerce Street, Glasgow G5 8DR).

Cosmetics and toiletries

Naturally Californian

Avocado oil and lemon fragrance are two of the major ingredients of the latest duo from Max Factor, the California Naturals. These complementary products are Avocado Lemon cleansing facial (£0·70) which is said to be rich enough to double as a night cream, and Avocado Lemon moisturiser, also £0·70, which is an all over moisturising treatment for face, hands and body. Both preparations are pale green in colour which is reflected in the design of the containers.

Also just arrived from Max Factor are four new shades of California sunsticks (£0·39), Clearly Red, Bronzed Burgundy (plum-red), Clearly Cinnamon (cinnamon brown) and Sunchilled Raspberry, and four new nail tint shades (£0·32), Raspberry, Chili Pepper (terracotta), Honey Grape (damson pink) and Cinnamon (Max Factor Ltd, 16 Old Bond Street, London W1X 4BP).

Photographic

Polaroid Copy Kit

An inexpensive Instant Copy Kit and accessories, providing a complete photographic copying system, is being introduced by Polaroid.

Both the copy kit and accessory unit are designed for use with any of three Polaroid Land instant picture cameras—Colorpack II, Colorpack III or Colorpack 80 and can be supplied with, or without, any of these.

The Polaroid 105-I Instant Copy Kit (£38·95 is a 2/3 : 1 reduction unit which answers a need to instantly and economic-

ally copy photographs, drawings, charts, extracts and similar items. It comprises: copy stand, close-up lens in mount, blue filter (for colour film used with tungsten light), polarising filter (for flash only), a Colorpack 80 instant picture camera and an attractive carrying case designed to hold the entire kit. Without the Colorpack 80 camera, the Kit retails at £24. The 106 Instant Copy Kit accessory unit, comprising a copy stand and close-up lens for 1/3 : 1 copies, will cost £15 (Polaroid (UK) Ltd., Rosanne House, Welwyn Garden City, Herts.).

Sundries

Jacquelle hairbrushes

Jackel will be delivering from mid-August their new range of Jacquelle hairbrushes, which are available in three styles Ballerina, Paddle and Semi-radial and come in pink, blue or black with a nylon filling (Ballerina and Paddle £0·39) and semi-radial £0·49) or wild boar bristle, (£3·75), which are hand-drawn on macassar and ebony wood back. Each of the latter comes with its own cleaning brush and is displayed in a counter merchandiser containing 12 units. (Jackel & Co Ltd, Kitty Brewster Estate, Blyth, Northumberland).

PRESCRIPTION SPECIALITIES

CALCITARE injection

Manufacturer Armour Pharmaceutical Co Ltd, Hampden Park, Eastbourne, Sussex
Description Vials each containing calcitonin of porcine thyroid origin 160 MRC units with vials of gelatin diluent. Injection intended for intravenous use is supplied with vials of saline-acetate diluent
Indications Paget's disease of bone, hypercalcemia of varying aetiology
Dosage Paget's disease: 0·5-2·0 MRC units/kg/day by intramuscular or subcutaneous injection. Hypercalcaemia: up to 4 MRC units/kg/day by intramuscular or subcutaneous injection
Precautions In patients with a history of allergy, a scratch (or intradermal) test should be conducted prior to administration
Notes Calcitonin for intravenous administration (50 MRC units/vial) is also available
Side effects Initial treatment may produce transient nausea, tends to disappear with continued treatment
Storage Below 25°C
Packs Boxes of 5 vials (£19·75 trade) and 10 vials (£35·50). 1 vial for intravenous use (£1·90)
Supply restrictions P1, S4B
Issued August 4, 1972

CHLORAMPHENICOL Minims

Manufacturer Smith & Nephew Pharmaceuticals Ltd, Bessemer Road, Welwyn Garden City, Herts
Description Minims containing a clear colourless solution of chloramphenicol 0·5 per cent
Method of use Instil one or more drops as required into the affected eye
Packs Boxes of 20 (£0·59) and 100 (£2·35)
Supply restrictions TSA
Issued August 7, 1972

PROMOTIONS

Dextrosol merchandiser

A merchandising unit has been introduced for Dextrosol, which enables the pharamcist to display together all four varieties of the product—natural, orange, lime and lemon.

Although sales are said to have risen overall by 17 per cent in the past year, the company believe many chemists have missed out on this growth through not stocking all flavours, so this unit is intended to help overcome the problems of restricted display space (CPC (United Kingdom) Ltd, Claygate House, Esher, Surrey).

Adagio unit and bonus

Fiona Sands are now distributing a new display unit which takes up less than a square foot of space and holds six products in the Adagio range.

During the introductory period, the company are also giving six perfumes (value £4·80) free to each retailer ordering one of the units and six of each of the six products displayed—perfume, fragrant mist, cream perfume, skin perfume, talc and the new foam bath. This offer is open until September 8 (Fiona Sands, Queens Way, Croydon CR9 4DL).

Skin care booklet

Winthrop Pharmaceuticals have produced a booklet called *Skin Care*, which discusses the skin and its functions in simple terms in relation to diet, hair, and make-up as well as cleansing and moisturising. Other aspects covered are the pH factor and the conditions acne and dandruff, in the light of the connection between them. Copies of the booklet are available free of charge (Winthrop Pharmaceuticals (Dept PR), Winthrop House, Surbiton, Surrey).

Glaxo sponsor walk

Glaxo were one of the main sponsors of a recent marathon walk to raise money for the Gainsborough St John Ambulance Brigade to equip a new ambulance. The walker, a local resident, included Glucodin and Complan in his basic diet, but unfortunately had to withdraw after 80 miles in 20 hours, having been hampered by bad weather (Glaxo Laboratories Ltd, Greenford, Middlesex).

Consumer offers

☐ 25cc trial size of Ma Griffe parfum creme at £0·55. 25cc Miparfum at £2, instead of £3·35. A sample size of Miparfum banded to the 55cc Ma Griffe eau de Cologne £2 (Parfums Carven, franchise division, Shulton (Great Britain) Ltd, Trevor House, 100 Brompton Road, London SW3).

☐ A handbag size wallet for one or two Fastidia mini pads in each pack, available until mid-August or when stocks of 200,000 packs are exhausted (Lilia-White (Sales) Ltd, Charford Mills, Birmingham 8).

☐ From August 7, a flashed "1½p off" Dixcel for men, Dixcel white and multicolour family tissues (British Tissues Ltd, Brougham Road, Worthing, Sussex).

☐ Three Breck beauty kits on sale from the end of August: 70cc shampoo for normal hair and 65cc pink creme rinse at £0·33 (value £0·39); 70cc Breck Basic texturising shampoo and 120g Miss Breck unperfumed hairspray at £0·44 (value £0·52); 70cc herb shampoo and 120g Miss Breck superhold hairspray and 65cc Blue creme rinse at £0·58 (value £0·68). On sale from the end of September a free sachet of Breck creme rinse with the 70cc and 112cc sizes of Breck Basic texturising shampoo (Shulton (Great Britain) Ltd, Trevor House, 100 Brompton Road, London SW3).

☐ Any record from the BBC top ten single record charts in exchange for two "free record" labels from US anti-perspirant or US herbal bath. The offer is limited to 12,000 records, after which vouchers worth 5p off the next purchase of a US product will be despatched. The offer is open until March 31, 1973 (Johnson Wax Ltd, personal care division, Frimley Green, Camberley, Surrey).

ON TV NEXT WEEK

Ln = London; M = Midland; Lc = Lancashire; Y = Yorkshire; Sc = Scotland; WW = Wales and West; So = South; NE = North-east; A = Anglia; U = Ulster; We = Westward; B = Border; G = Grampian; E = Eireann; CI = Channel Islands.

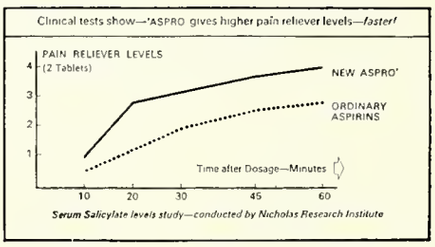
All Fresh: Ln, M, WW, So, We, B, CI
Aquasil: So
Brylcreem: All except U, B
Calgon: So
Clinomyn: So
Close-up: All except E
Cool: Ln, WW, So
Eno: Ln, M, Lc, Sc, WW, So, U
Harmony hairspray: All except E
Lil-lets: Ln
Macleans Fluoride: NE
Poligrip: M, Lc, Y, Sc, So, NE, G, CI
Rennies: All except U, E
Saxin: Ln, M, WW, A
Setlers: All except Y, W, B, E, CI
Shield: All except E
Signal: All except E
SR: All except E
Sunsilk hairspray: All except E
Sure: All except E
US herbal bath: All except U, E
Vosene: All except E
Zoflora: M, Lc, Y, NE, U
Zubes honey & lemon sweets: M, WW, So

We couldn't make anything better than aspirin.

So we made aspirin better.

Aspro is aspirin in highly refined form. Manufactured under stringent conditions of quality control. And *microfined* to ensure rapid absorption.

Aspirin must go into solution in the stomach before it can be absorbed into the bloodstream and start relieving pain. Because Aspro is microfined it dissolves much more quickly and is, therefore, absorbed into the bloodstream much faster. Thus Aspro gets more pain reliever into the bloodstream in the first important minutes than Ordinary Aspirin B.P.



Clinical tests prove that the average salicylate concentration obtained with two tablets of Microfined Aspro is 129% higher 20 minutes after ingestion than with Ordinary Aspirin B.P.

Microfined ASPRO, ASPRO SOLUBLE and ASPRO JUNIOR all contain microfined aspirin.

We couldn't make anything better than aspirin. So we made aspirin better.

ASPRO. Pain relief, pure & simple.

ASPIRIN TODAY:

A creditable past—a glorious future

Killer, potential life-saver, safe-in-use home medicine, hazardous and harmful drug. All those descriptions could be used accurately in talking about the ubiquitous aspirin—it depends upon where you stand and your "vested interest". In the course of this article, we propose to examine the various viewpoints and, hopefully, put some of them in perspective.

The history of aspirin goes back into antiquity. The discovery date normally quoted is 1897, but in fact this was the date of the production of acetylsalicylic acid in a chemically pure and stable form. Hippocrates himself knew of the analgesic and anti-pyretic action of the willow-tree bark but the knowledge of this herbal treatment was half-forgotten over the centuries and only revived in the 19th century. Various scientists at that time produced salicylic acid, initially from the willow tree bark and later by chemical synthesis. However, these substances—used for the treatment of rheumatism—were badly tolerated by patients and had a vile taste.

Among the patients managing to tolerate the drug was the rheumatic father of Bayer chemist Felix Hoffmann. Stimulated by the plight of his father, Hoffmann researched into salicylic acid compounds. In 1897 he succeeded in producing acetylsalicylic acid in a chemically pure and stable form, which was much better tolerated.

Bayer were quick to realise the value of the compound—their second important pharmaceutical discovery (the first was phenacetin). In 1899 they named and registered it Aspirin because the chemical name was cumbersome. The "A" came from acetyl and the rest of the word from *Spirea ulmaria*, a plant in the meadowsweet family. Aspirin tablets very quickly entered world markets. By 1906 the trademark was registered internationally and even today "aspirin" is a registered trademark of Bayer in more than 70 countries, although the events of the 1914-18 war made it generic in the UK.

Already in 1902, Burroughs Wellcome & Co were advertising Tabloid Aspirin in the *C&D Diary*, but in the 1904 edition, supply had been transferred to the Standard Tablet Co.

The Bayer Co themselves first advertised the mark in the 1905 *Diary* as "a substitute for the salicylates" and later, until 1913, as an anti-rheumatic, offering powder, tablets and compound tablets with caffeine, quinine or phenacetin. Also available was aspirin "soluble powder".

But with the outbreak of hostilities, the new drug became freely available in Britain and even the 1914 *Diary* had three entries under the heading "acetyl salicylic acid"—from Roche, Alliance Drug Chemical Co, and Chas Zimmermann & Co. Alfred Bishop Ltd offered "patented" soluble salts of acetyl salicylic acid.

In 1915 aspirin came into use as a "generic" name in the *C&D Diary*.

First to recognise the enormous potential of the brand name in marketing aspirin—a truly active drug that could live up to its claims—were the makers of Aspro, who took over where Bayer had been forced to leave off. Gollin & Co Pty Ltd, with offices in Mincing Lane, took a page in the 1926 *Diary* to tell pharmacists that "Every day is an Aspro day"—promising increased turnover as a benefit of an advertised brand and proclaiming "Aspro —Australia's biggest seller—make it yours". The pharmacist was not impressed, however, preferring the "generic" version. The Aspro company, determined to repeat their Australian triumph, were forced to court the grocer, and representatives actually paid the grocers' medicine licence fees to encourage them to stock the product (in those days they were reluctant!).

It is perhaps possible to reflect that medicines distribution, today might be different had pharmacists in 1926 kept their hands on such proprietaries.

Drug of choice

Last year, the council on drugs of the American Medical Association described aspirin as the drug of choice when a mild analgesic or antipyretic is indicated, and the primary agent used in the management of some rheumatic diseases. Aspirin, said the council, is "more useful in treatment of headache, neuralgia, myalgia, arthralgias, and other pains arising from integumental structures than in acute pain of visceral origin, but may be effective in less severe postoperative and postpartum pain or in pain secondary to trauma and cancer. In the latter, aspirin may provide adequate relief and should be tried prior to use of more potent drugs . . . When drug therapy is indicated for reduction of fever, aspirin is one of the most effective and safest drugs".

The strength of this recommendation was shown in a paper published in the *New England Journal of Medicine* in April this year. Fifty-seven patients with mild to moderate pain problems resulting from unresectable cancer took part in a double-blind crossover study of nine oral analgesics and placebo, aspirin, in a single dose of 650mg came out top of the list whether judged by the proportion of patients claiming greater than 50 per cent relief at any time during six hours after administration, by the mean percentage of analgesia claimed by the patients, or by the relative "ranking" of each drug by the patients. This trial also showed up one of the investigators' problems in that 21 per cent of these patients with unquestioned pain claimed more than 50 per cent relief from the placebo. Patients who experienced side effects with placebo reported twice the frequency of side effects with active drugs—and they also tended to be the ones who obtained a placebo analgesic effect.

Arguing in favour of aspirin, the authors say: "It has been our own experience that if aspirin is recommended with the strong endorsement of the physician, it is acceptable to even the most sophisticated patient."

Adverse reactions

If aspirin is one of the older effective synthetic drugs, it is also one of the most researched. And one aspect that has continually divided the researchers is the relative potential for side effects possessed by the various forms. The pharmaceutical industries of the world have tried all manner of means to perfect the drug by formulation and presentation—probably because the starting point is itself so much nearer perfection than most competitors that it must seem but a short step to the ultimate product. But perfection is elusive, and for almost every claim of a breakthrough there is a counter claim of "no

Continued on p 191

Felix Hoffmann synthesised aspirin

Resale Price Maintenance

Two years ago the Restrictive Practices Court ruled in favour of allowing prices of Proprietary Medicines to be maintained being of the opinion that by so doing the best interests of the public would be served.

Consistent with the decision of the Court, Miles Laboratories have continued their policy of upholding price maintenance in respect of the retail prices of their medicinal products and have actively sought the co-operation of the distributive trades to achieve this end.

We would like to take this opportunity to record our appreciation of the co-operation of the majority of our customers in observing this policy and to reaffirm our intention of taking action against persistent price-cutters.

MILES

MILES LABORATORIES LTD CONSUMER PRODUCTS GROUP
ALKA-SELTZER* ALKA-MINTS* GLUCA-SELTZER* ACTRON*

*trade mark

Miles Laboratories Ltd., Consumer Products Group, Stoke Court, Stoke Poges, Slough, Bucks.

ASPIRIN TODAY

Continued from p 189

apparent advantage over the standard preparation". The probable explanation is that there is almost as much deviation between the "standard" versions as there is between the standard and the "improvement" in many cases.

Two other factors are of importance, and are commented upon by the authors of a paper substantiating the superiority of Bufferin over plain aspirin. They found that with all their controls on the accuracy of the analytical method, there was a person to person variation in aspirin absorption that had to be controlled by a "cross-over" design in the experiment. Also, aspirin absorption varied in the individual from day to day.

Gastro-intestinal side effects have long been recognised, leading to the development of soluble forms, buffering, hastening of stomach emptying, enteric coating, etc. It is here particularly that the truth is buried in a welter of trial reports—indeed, one could carry out statistical analysis on the basis of numbers of papers alone!

Buffering is perhaps the best example of this "pay your money and take your choice" situation. Two reputable and well-quoted trials have shown that salicylate blood levels can be double those achieved with plain aspirin (one of them found the same with soluble aspirin BP) at times up to half an hour after ingestion, but others record indistinguishable analgesic effectiveness and gatro-intestinal tolerance. The AMA reaction was that there has been no conclusive evidence to support the giving of buffered aspirin.

Action uncertain

Even the way that aspirin causes gastric reactions remains uncertain. Theories have been put forward relating to local action of crystals (though some "soluble" forms and parental aspirin can cause blood loss), mucosal cell damage during drug absorption, and inhibition of prostaglandins (see later). Certainly, there is more than one factor, and alcohol ingestion is among those that will increase the haemorrhage with most aspirin preparations.

Since many trials have shown little difference between most forms of aspirin in relation to gastric irritancy, Aspro produced their "microfined" version in 1965 to obtain faster absorption (reducing stomach contact time) and providing the patient with the alternative of a tablet to swallow, or take in water, all in one presentation. The importance of particle size in relation to absorption has been well documented, and Aspro found that they could achieve levels approaching those obtained from a solution of aspirin, and 20-minute serum salicylate levels $2\frac{1}{4}$ times those of a typical aspirin tablet BP.

However, the same order of improvement in absorption and serum levels had already been achieved by calcium aspirin —though the claims in relation to gastric irritancy are again a matter of dispute according to which scientific papers you read. That the public have been persuaded there is merit in taking aspirin dissolved in water rather than in suspension may be judged by the fact that Aspro Soluble came onto the market in 1970.

Although calcium aspirin in solution has long been thought to have advantages, it was not until the Disprin formulation was introduced in 1948 that a stable tablet was available on the market. It quickly gained acceptance by the medical profession—a point made strongly in advertising—and was adopted as the Pharmacopoeial form in the 1955 Addendum to the 1953 edition.

It seems likely that medical acceptance has been based on the view that, although superiority may be hard to prove, it is theoretically probable and it is therefore better to play safe. The patient can almost certainly be relied upon to dissolve a soluble aspirin tablet but ensuring the crushing of an ordinary BP tablet—said to be necessary to achieve the same effect—is much more difficult.

Not an 'aspirin'

A much earlier type of "soluble aspirin" was Alka-Seltzer, first marketed in the 1930s. However, the makers emphasise that it cannot really be regarded as an "aspirin" product because, when dissolved in water as it must be, the solution contains sodium citrate, sodium acetysalicylate, a small amount of residual sodium bicarbonate and dissolved carbon dioxide. The salts of a weak acid and a strong base ensure that the solution has a highly effective buffer system. This so fundamentally affects the properties of the aspirin content of the dry tablet that most of the criticisms of the parent drug must be assessed anew.

There is a great deal of published evidence that the Alka-Seltzer solution formula produces no increase of occult blood over the normal. Because of the elevated pH, the buffer capacity and the hastening of gastric emptying, the sodium acetylsalicylate is absorbed in the small intestine and not in the stomach and high plasma acetylsalicylate levels are achieved more rapidly than with aspirin BP tablets. However, the absorption of antacid renders the urine sufficiently alkaline to increase the excretion rate and ensure that toxic salicylate levels do not build up.

With all these advantages (as an analgesic), why is the product sometimes "misunderstood" in professional circles? Probably because the significance of the product's antacid buffering capacity is not appreciated and because the reference to "upset stomach" may be wrongly interpreted to include a chronic stomach condition. The makers are careful to specify only the acute effects of "over indulgence". Their claim here is the alleviation of the symptoms to the complete syndrome (the upset stomach and headache) for the normal person who is "temporarily indisposed"—as distinct from the treatment of any disease condition. The rationale is rapid antacid action, high buffering capacity and stimulation of gastric emptying—coupled, of course, with the analgesic effect of the acetylsalicylate.

A less obvious bonus with this antacid formulation is that aspirin poisoning is most unlikely—children could not chew the tablets in quantity because of the excessive unpleasant effervescence in the mouth and, if taken in solution, the emetic effect and salty taste of several tablets would induce nausea and vomiting.

Although its long-term high dosage use in rheumatoid conditions, etc, is precluded by the high sodium content and the increased rate of renal excretion, several authorities have recommended effervescent aspirin as the formulation of choice for occasional analgesia.

Any reviewer of the published work on aspirin cannot help but be struck by the number of papers that depend for their conclusions on assay of plasma salicylate levels. Aspirin itself is rapidly hydrolysed once absorbed, and there is evidence to suppose that this is the reason for the relative brevity of its analgesic action—the effectiveness ratio of acetylsalicylate to salicylate has been put as high as ten to one for antipyretic and anti-inflammatory properties, and it has been suggested that the analgesic effect resides almost exclusively in the aspirin molecule. Microencapsulated aspirin has been an attempt to overcome this problem by releasing drug at a steady rate from shortly after ingestion, which has been shown to produce significant blood levels of acetylsalicylate over a longer period than from the same dose of "ordinary" aspirin.

The position on adverse reaction to aspirin was studied in some detail and put into clear perspective by the 1971 "mild analgesics" report of the AMA council on drugs, from which we quote:

"Adverse reactions from usual doses of aspirin occur infrequently; most common are gastrointestinal disturbances (dyspepsia, nausea, vomiting, and occult bleeding).

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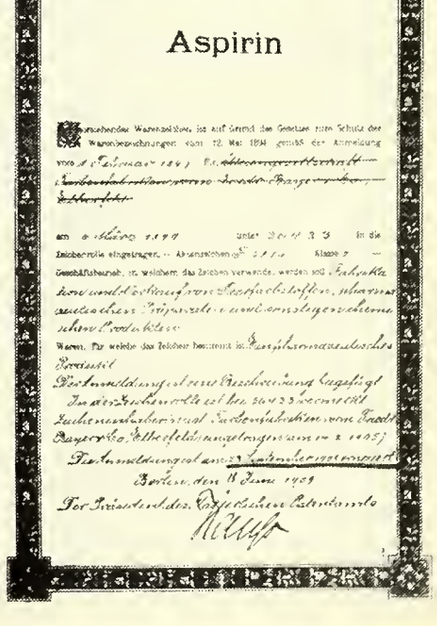
Bayer's trade mark certificate



Aspirin

Berlin, den 11 Juni 1909

Der Präsident des Kaiserlichen Patentamts

ASPIRIN TODAY

Continued from p 191

With prolonged administration, occult bleeding may lead to iron deficiency anaemia. Gastrointestinal effects may be diminished by taking aspirin with milk, food, or large quantities of water. Use of enteric-coated preparations will reduce gastrointestinal effects, but absorption of aspirin will be delayed and may be quite variable. Massive gastrointestinal haemorrhage occurs rarely and, although its relationship to history of peptic ulcer is uncertain, use of a non-salicylate may be preferable in high-risk patients. Large doses may cause an increase in prothrombin time, but this is not clinically significant unless patients are taking anticoagulants. In the small number of individuals who appear to be hypersensitive to aspirin, even usual doses may cause skin eruptions or severe urticarial or asthmatic-type anaphylactoid reactions. Patients with asthma, hay fever, or nasal polyps have a higher incidence of these reactions; thus, they should avoid aspirin and aspirin-containing products.

"During therapy with large doses for prolonged time (eg, in rheumatic disorders), signs of salicylism (tinnitus, head ache, dizziness, confusion) may occur, but these may be controlled by modifying dosage. Acute intoxication from accidental poisoning is not uncommon, particularly in children. Toxic doses cause a disturbance of acid-base equilibrium, usually manifested as a metabolic acidosis in infants and young children and as a respiratory alkalosis in older children and adults; hyperthermia may also occur in infants and young children. Severity of intoxication should be determined by measuring blood salicylate level."

It will be seen from this succinct statement that aspirin receives a pretty clean bill of health from the AMA—one to which critics of general sale must find an answer if they are to hold sway.

About one in 500 may show some form of sensitivity to salicylates, it has been estimated, but serious blood loss with vomiting is a very rare occurrence. This seems to be one of the few absolute contraindications to the use of aspirin—though there are other situations in which it is obviously best avoided. Any form of severe haemophilia is also given as a complete contraindication.

The drug passes the placental barrier, but there have been no papers in recent years to inciriminate aspirin as a teratogenic agent.

Paracetamol, aspirin's main rival in the o-t-c analgesic field, has its problems. At an inquest earlier this year on two women, a pathologist warned that 25 tablets could cause fatal liver damage and a stomach pump could not be used in treatment, as symptoms do not appear for some three days after ingestion. It is understood that in some countries the drug is restricted to prescription or is banned altogether.

Recently, Sterling-Winthrop have attempted to overcome the gastric problems of aspirin by synthesising an esterification product of paracetamol and aspirin, known as benorylate (*C&D* July 15, p 73).

Advertising

Given an effective drug to sell, early advertising of aspirin was perhaps less restrained than prudence and ethics should have dictated, and there can be little doubt of the need for the voluntary controls that followed.

The British Code of Advertising Practice precludes any product being promoted in terms that could lead to its use as a treatment for insomnia or rheumatism, where the reference is to chronic or persistent. But it is the code specifically drawn up by the Advertising Association in 1962 to control analgesics advertising that is most relevant. In its preamble, it said that factors such as increasing competition, increasing "drug-mindedness" by the public, the advent of the tranquilliser era, and progress in pharmaceutical presentation, had encouraged advertisers to seek new and more dramatic claims for their products "and in so doing some have attributed properties to them that are not compatible with scientific principles".

The following points were stressed particularly as needing to be avoided:

☐ Exaggerated claims about the speed with which a product can relieve pain. Without reliable clinical evidence there should be no suggestion that pain can be relieved in under 10 minutes.

☐ Vague, unsupported and undefined references to safety.

☐ Statements that a product does not contain a drug in common use—which might imply that the other drug was harmful.

☐ Unsubstantiated inferences that because a drug is useful in relieving one kind of pain it is useful in relieving other kinds of pain.

☐ Exaggerated claims or inferences about the certainty and speed with which a product can relieve colds or influenza, or reduce a fever or raised body temperature.

The code published for the guidance of television advertisers goes a little further again. It warns that an analgesic should not be advertised so as to imply that it is in any sense a "pick-me-up", or that it should be taken when feeling generally unwell, depressed or tired. No suggestion may be made that the product should be carried round like a lozenge or sweet ready to be taken when required, and the importance of correct dosage should be indicated whenever possible.

Two other points are noteworthy—permission in the code to refer to safety in relation to upset stomachs, provided this can be fully substantiated, and prohibition of the advertising of children's analgesics before 9pm.

Television has been a popular medium with the analgesics manufacturers—Nicholas Products say this is because "faith and assurance" are being sold, and these aspects come over particularly well on the screen. However, as TV costs go up, Press advertising increases.

Aspro concentrate on selling the single ingredient—"All your headache needs" is the message—to contrast with those products which stress the number of ingredients they contain. The advertising platform is also restricted to the treatment of headache, in the belief that the product once in the home will be used for the other indications. There is a strong appeal to women, because they make most of the household purchases.

There is a tendency for analgesics advertising to continue unchanged for fairly long periods—again, this is part of the process of building up the purchaser's confidence in the product, in which continuity and frequency of message are key factors.

Some impression of the importance of aspirin to the o-t-c industry can be obtained from the fact that the Proprietary Association of Great Britain has a technical committee dealing specifically with this drug, and it is the PAGB membership that imposes upon itself, an even stricter voluntary code than either the law or the advertising industry demand.

Labelling restrictions

The PAGB vets all its members' advertising literature and product labelling. Labels of all analgesics, it decrees, must bear a warning that if symptoms persist, a doctor should be consulted. Also the dosage instructions, which must be clearly laid out, must indicate a limit of either the number of doses or the total of tablets that may be taken in a day. There is also a guide to the maximum doses that should be recommended and a method for calculating the dosage of compound analgesics.

If the product is not to be recommended for children, a "cut off age" must be indicated below which it should not be taken. For children there is a detailed dosage schedule for different age groups, and a warning that the product should not

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Bayer's first aspirin pack, 1899

ASPIRIN TODAY

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be used for more than 48 hours—because of excretion problems. This dosage was worked out in conjunction with the Committee on Safety of Drugs. There is, of course, a standard recommendation that analgesics should be labelled "keep out of the reach of children".

The strip pack is being widely adopted for aspirin in the o-t-c industry because of the protection that it affords the product. It also has safety advantages, and PAGB members are far from convinced that child-resistant closures will be the answer to poisoning. They argue that it would be difficult to know which products should be packed with safety closures and fear public reaction on the safety of products not required to have such closures. However, the PAGB is represented on the BSI committee which is producing a standard for safety closures—though they believe the answer will lie more in better education of the public about storage precautions, and feel the Department of Health has an important rôle to play in this matter.

In the United States, aspirin was the first item to be specified under the Poison Prevention Packaging Act when earlier this year the Food and Drug Administration required that all products should be supplied in "child-resistant" packages.

Point of sale

One thing that the o-t-c industry would very much like to know—as would the profession—is how aspirin will be placed in relation to the general sale list under the Medicines Act. The Medicines Commission committee which has this under consideration is believed to have studied many thousands of products, hence the length of time being taken to reach a decision. Meanwhile, the industry is pressing for the publication of an interim report on progress so that it can plan ahead—they want this report in the Autumn.

There is plenty of evidence to support the profession's case for restriction—but some very fair points can be made by opponents. In an ITV "World in Action" programme last November, much was made of a patient with a duodenal ulcer who had been treating himself with Alka-Seltzer. It was claimed that a survey had shown that 78 per cent of those regularly taking Beecham Powders did not know they were taking aspirin, and for Aspro the figure was 56 per cent, Anadin 58 per cent, Alka-Seltzer 90 per cent.

During the same programme it was also said that 6 per cent of iron deficiency cases referred to hospitals were associated with aspirin ingestion, and that aspirin was the cause of a quarter of admissions of patients vomiting blood. The latter figure has been put at 7,000 (one-quarter of 28,000, of whom 250 die) each year. It is factors such as these that have led some of the doctors who have to deal with the consequences of analgesics misuse, to call for their restriction to pharmacies.

But the industry regards sales of aspirin as one of the best examples of the need for "convenience" in purchasing. They point out that although the pharmacy is the primary place for the public to purchase medicines, people need to be able to buy when they get symptoms—they don't always have stocks in the house. Even in the home counties, they say, it is possible for the nearest pharmacy to be 3-4 miles away—and there are only just over 12,000 pharmacies, but 100,000 other outlets. This convenience of purchase is regarded as particularly important to mothers of young children and to the elderly.

If the patient wants advice, she will go to the pharmacy rather than any other outlet, it is claimed, but as a rule the pharmacist allows the customer to purchase without questioning if she knows what she wants—so why should she not make the same choice equally safely at the grocers? It is this aspect of self medication without any professional intervention that makes the industry put its faith in education through labelling. Again it is pointed out that the product may be bought on behalf of someone else, and any warning may not be conveyed to the patient. Also it may be purchased against eventualities, and the warning will have been forgotten when the symptoms arise; or the product may be used by someone other than the purchaser.

The answer therefore is seen to lie in cautionary labelling—which is with the medicine no matter who purchased it, when, or where. And the PAGB code requires the term "aspirin" to be used in connection with every product containing it—so it's more a matter for educating the customer to read labels!

Combined therapy

A great deal of o-t-c aspirin is sold in the form of a mixture of analgesics—whether it be generic APC or codeine co, or one of a plethora of proprietaries. Some idea of the scale can perhaps be seen from the annual £630,000 said to be spent on Anadin (*Retail Business* September 1971) putting it second in the total home medication market.

And like every other aspect of the aspirin story, there are two sides to the coin. The AMA council on drugs claimed there is a "paucity" of information on interactions between these drugs, and concluded that "mixtures of analgesic-antipyretic agents are irrational and use of these mixtures is not recommended."

However, this assertion must be viewed against a current American "witch-hunt" against combination drugs in general—an attitude that has somewhat mellowed in recent months with the admission that there are perhaps occasions when a combination product is to be tolerated if not welcomed. Certainly there have been some frightening estimates of the number of tablets that would be needed to replace all combinations by single-drug dosage.

But on the home medication front, where the aim is always symptomatic relief, the fixed dosage combination is probably essential. Usually there are several co-existing symptoms, and it would be both impracticable and undesirable for the patient to start to do his own "mixing"—there are already enough problems with interaction with prescription medicines.

The Committee on Safety of Medicines looks very carefully at the potential hazards of o-t-c drug combinations, but on the whole the industry is probably right to claim that the combination that has been subject to full clinical testing—*as* a combination—is safer than indiscriminate mixing. A good example of the "symptoms package" has of course been the introduction of "hot lemon" drinks for colds and 'flu, some being based on aspirin as a major ingredient.

One important exception to the AMA council on drugs rule is in relation to the mixture of aspirin with codeine. Here, because of the difference in mode of action, the analgesic effects are known to be additive. The main advantages are said to be greater degree of pain relief and a reduced effective dosage of codeine.

The attitude of the o-t-c aspirin manufacturer is perhaps well summed up by this quotation from "Apothecary's Venture", a book that describes the research effort of the international Nicholas organisation—"There have been tragedies, though as a suicide weapon aspirin is far less efficient than a rope or carving-knife. There have been accidents, both in and out of professional care, but the latter have nearly always been due to failure to follow instructions. And in general it is overwhelmingly clear that acetylsalicylic acid is devoid of side effects when used as a self-prescribed analgesic, and that few are unable to tolerate even the massive doses (up to ten times these recommended for home therapy) used in the professional treatment of rheumatism. . . . Few of medicine's—few, even, of mankind's—discoveries have been so, wholly beneficial."

Formulations

The undoubted place of aspirin at the centre of long-term rheumatic pain relief has provided a real challenge to the formulator. Although there may be dispute about the importance of the gastric "irritation" and occult blood loss, any prescriber would prefer to eliminate these hazards. The rationale for some of the formulation development is set out below.

Caprin (Sinclair Pharmaceuticals)
Here the formulation is based on a mechanical concept, reversing the usual rapid-disintegration aim. The tablets are produced under heavy pressure, resulting in a tablet that will not disintegrate in the stomach. The possibility of surface erosion or diffusion in an acid medium

has been overcome by the application of a long-chain polymer to the aspirin prior to compression. This polymer has the property of being resistant to acid but swells up on contact with alkali. This, say the makers, together with the acid-alkali interaction between aspirin and the alkaline medium of the duodenum, provides rapid disintegration and absorption.

Aspergum (White Laboratories)
An orange-flavoured chewing gum presentation which provides an original method of administering aspirin to children, besides being valuable for adults who find it difficult to swallow tablets. However, the product is primarily indicated for the local presentation of aspirin after tonsillectomy, in acute pharyngitis and tonsillitis, and in dentistry. The rationale is that the action of chewing stimulates saliva flow, releasing the aspirin from the vehicle and delivering it in finely dispersed form to all parts of the oral cavity and throat.

Bufferin (Bristol Laboratories)
Formulation of aspirin with magnesium carbonate and aluminium glycinate. Published trials show that buffering with this combination not only reduces gastrointestinal side effects but also increases the plasma salicylate levels, by comparison with unbuffered aspirin. In one trial, 26 out of 37 hospitalised rheumatoid arthritics intolerant to aspirin were found able to tolerate Buffcrin, and in a healthy-subject study the product gave approximately double plasma salicylate levels at intervals from 10 to 30 minutes after ingestion.

Ekammon (WB Pharmaceuticals)
Contains, in addition to aspirin, acetomenaphthone and ascorbic acid. The principle is that the vitamin K counteracts the reduction in blood prothrombin level produced by aspirin, and the vitamin C the deficiency commonly found in rheumatic conditions. However, increasing evidence of the direct irritant action of aspirin on the gastric mucosa has led the makers to cease promotion of the product.

Paynocil (Bencard)
Contains aspirin 600mg and aminoacetic acid 300mg. For children Junior Paynocil (quarter strength).

The improvements conferred upon aspirin in this formulation are said to be threefold. First, it is twice the strength of aspirin tablets BP as well as being twice as rapidly absorbed. Second, the glycine content helps to distribute the aspirin rapidly into the stomach in fine particles which are themselves coated with glycine, thus minimising the risk of gastric irritation. This can be particularly helpful in the case of patients such as those with rheumatic disorders requiring large continuous daily doses. Thirdly, the glycine allows the tablet to disperse quickly on the tongue, masks the unpleasant taste of aspirin and thereby allows the product to be taken, if required, without water.

Levius (Pharmitalia)
Tablets of 500mg aspirin in micro encapsulated form. Each tablet consists of about 35,000 microcapsules loosely bound together in a friable tablet which rapidly distintigrates on contact with moisture.

After administration the drug is released by a process of diffusion through the ethylcellulose walls—each one can be regarded as being analogous to the cellophane dialysis membrane of a renal dialysis machine. Gastric juice, and later intestinal juice, diffuses through the thin polymer wall, dissolves a proportion of the aspirin to form a concentrated solution which then exerts a diffusion pressure on the inside of the wall. Since the wall is unyielding but permeable to aspirin, aspirin diffuses out through the micro-capsule walls into the gastrointestinal secretions, from which it is absorbed. This process of diffusion, which is basically an attempt to equalise aspirin concentrations on both sides of the ethylcellulose walls, continues until the contents of the micro-capsules are exhausted.

This method of presentation of aspirin is claimed to have two main pharmacological consequences. First, reduction of gastric irritation because with controlled release no part of the gastrointestinal tract receives the full irritation of the whole dose at any one time. Second, prolongation of analgesia through providing effective serum acetylsalicylate levels over a longer period than would result from administration of conventional tablets.

Prospect of many new indications

An effervescent aspirin without the excess alkali present in Alka-Seltzer is available on the continent it can be administered whenever aspirin is indicated—unlike the high-sodium preparations which are contraindicated in cardiac and renal diseases. Formulation is said to achieve high blood levels within 10 minutes of administration.

One of the most exciting prospects for aspirin at the present time is in the realms of preventing infarction.

Already there is a product on the market in Germany, though British opinion is that further long-term trials are required to prove the drug's value. Work is proceeding in coronary thrombosis, but conclusive results are not expected for a year or two. There are also studies on venous thrombosis, giving very small doses pre- and postoperatively. Here it has been suggested that there is already enough evidence to support the use of the drug in advance of long-term controlled trials on the basis that it appears to work and is unlikely to have adverse effects.

The dosage involved is of the order of 300mg per day—and it may transpire when studies are complete that 300mg per week is all that is necessary.

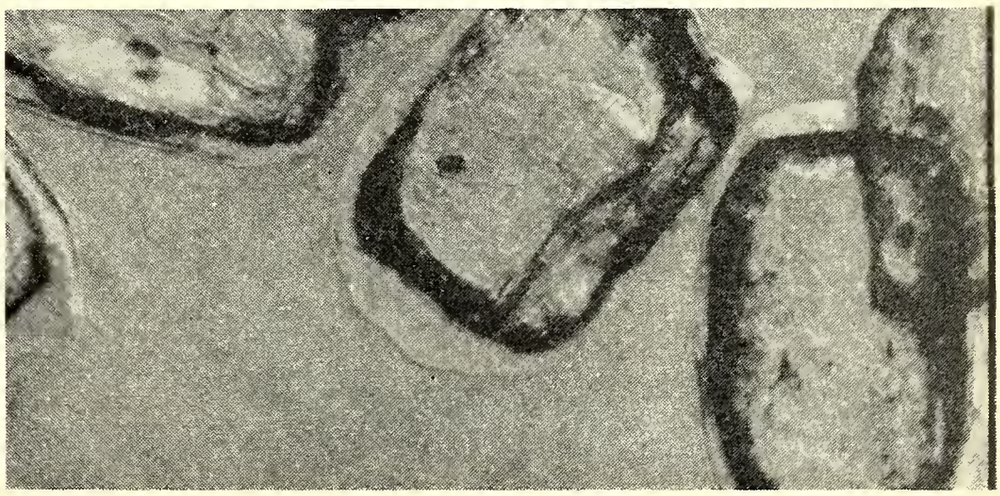
This effect—which is distinct from the direct anticoagulant effect of larger doses of aspirin—is achieved through interference with platelet aggregation by ADP and by collagen. It appears that prostaglandins are involved.

Aspirin may also have a place in the treatment of cholera, it has been suggested. Again it may be a case of interference with the prostaglandins, the hypothesis being that cholera toxin causes the release of massive quantities of prostaglandins. Several companies are showing interest in this application and some work is being done using intravenous aspirin with fluid replacement therapy.

Relatively few therapeutic trials of aspirin have set out simply to demonstrate the drug's efficacy—after three-quarters of a century, that is almost taken for granted. But with an estimated 2,000 tons—6,000 million tablets—being consumed annually in Britain alone, it can be assumed that aspirin has passed the most demanding of trials, that of long-term consumer acceptance. Indeed, it is probably only aspirin's genuine effectiveness that has enabled it to survive the worst indiscretions of its promotors in the past. That it has a long and valuable future in medicine is in little doubt.

Illustrations on pp 189, 191 and 193 courtesy Bayer Pharmaceuticals. That on this page, Pharmitalia

Microcapsules of aspirin magnified approximately 250 times



Aspirin and the prostaglandins

By Dr G. B. West

Aspirin remains a drug widely used in self-medication and yet the way in which it acts is still a mystery. Despite a variety of experimental models of inflammation, pyrexia, and algesia, no general theory is available to integrate all the effects of aspirin on these states. There is no doubt, however, that it helps to control the defence mechanisms of the body.

As it does not markedly prevent the formation or the actions of the well-known endogenous compounds which mediate inflammation (histamine, 5-hydroxytryptamine, kinins, slow-reacting substances), it may be that aspirin inhibits the synthesis or the effects of other less obvious precursors or mediators of defensive reactions. For example, the prostaglandins have been found in inflammatory exudates of different kinds and they do produce pyrexia.

First association

The exploration of antagonism between aspirin and prostaglandins dates back to 1964 when Berry & Collier reported that bronchoconstriction induced in guinea-pigs by injecting a particular prostaglandin intravenously was slightly reduced by appropriate doses of aspirin in this preparation.

Later, in 1968, Collier & Sweatman found that aspirin prevented the contraction of human isolated bronchial muscle induced by one prostaglandin ($PGF_2\alpha$) but was ineffective against the relaxation of muscle induced by another two prostaglandins (PGE_1 and PGE_2). In several other situations, aspirin was shown to antagonise the actions of arachidonic acid, now known to be a precursor of the prostaglandins.

Later still, in 1971, Vane and his colleagues reported that aspirin blocked the synthesis of PGF_2 and $PGF_2\alpha$ from arachidonic acid in cell-free homogenates of guinea-pig lungs, in the isolated perfused dog spleen induced by adrenaline, and in human platelets induced by thrombin, effects all occurring at drug concentrations within those attained in human plasma during oral treatment.

What are these prostaglandins? The original observation of their presence in cells was made in 1929, the same year that Burr & Burr identified certain fatty acids as being essential for growth, development and reproduction of rats. Many of the effects of deficiency of these fatty acids were traced to impairment of function of cell membranes. Then, in 1935, von Euler showed that an extract of seminal fluid of man, sheep and goat produced vasodilatation and contraction of certain other smooth muscle (gut and uterus), and because of its possible origin from the prostate gland he called the active material prostaglandin.

This material is now known to consist of a mixture of several closely related compounds which occur widely in mammalian tissues, although it was not until 1962 that their structure and their relationship with the certain fatty acids, considered essential for development, became clear. In fact, a complete understanding of the importance of the prostaglandins is yet to come.

All fatty acids are carbon-chain compounds ending at one end of the chain in a HCOOH group. The most common chain length by far is 18 carbons; the saturated compound, then, is stearic acid whereas the mono-unsaturated compound is oleic acid, with the one double bond residing at the centre of the chain (between C9 and C10). Both animals and plants can desaturate oleic acid further and so introduce further double-bonds into the molecule.

The prime essential fatty acid for animals appears to be linoleic acid, a C18 acid with 2 double-bonds residing at C6 and C9, other fatty acids being made from linoleic acid to provide energy or part of the structure of the cell membranes. The key acid is now considered to be arachidonic acid, a C20 acid with 4 double-bonds at C6, C9, C12 and C15, and this is formed from linoleic acid by introducing first the third double-bond at C12 to yield linoleic acid and then elongating the chain length by two carbons to form homolinolenic acid before introducing the fourth double-bond at C15 (see formulae).

Membrane constituent

Linolenic acid and arachidonic acid are still classed as essential fatty acids as they can prevent the classical symptoms of deficiency, and now homolinolenic acid has been added to the list. For the most part, these essential fatty acids are combined as glycerides or phospholipids; arachidonic acid, for example, playing its role as a major acid in a phospholipid contained in cell membranes.

These unsaturated fatty acids are highly susceptible to oxidative processes and when oxidation occurs at specific points with ring closure at the centre of the chain the prostaglandins are formed. The animal body is continuously oxidising some of its reserves of essential fatty acids and the prostaglandins so formed contract smooth muscle, lower the blood pressure, and reduce blood platelet stickiness if enough is produced.

Unsaturated fatty acids and oils containing them (for example, corn oil, cotton seed oil, and soya bean oil) are often prescribed to lower blood cholesterol levels in patients with hypercholesterolaemia and to reduce the symptoms of atherosclerosis and cardiovascular disease, two major causes of early death in the developed countries.

When lipid peroxidation of these unsaturated fatty acids takes place, the structure of cell membranes and subcellular organelle membranes becomes disorientated. Moreover, in inflammatory states, enzymes such as phospholipase A are activated and the fatty acids released from the cell membranes become oxidised, with the formation of peroxides leading to the prostaglandins. Oxidation of homolinolenic acid yields prostaglandin E_1 which differs from prostaglandin E_2, derived from arachidonic acid, only in the absence of a double-bond at C15 (see formulae). In the F series of prostaglandins, there is a hydroxyl group at C12 in place of the keto group in the E series. When the membrane of the lysosomes breaks under oxidising reactions, for example, the released hydrolytic enzymes then multiply the original damage by affecting other cells and so the area affected becomes extensive. Intact lysosomes which remain try to ingest damaged membranes which they cannot adequately metabolise and so pigments gradually develop. These so-called age pigments (for example, lipofuscin) accummulate in the heart, brain and muscle of aged persons, and the finding of peroxidised fatty acids in age pigments points strongly to the involvement of lipid oxidation processes.

Anti-oxidants

To control these oxidative processes leading to the formation of prostaglandins, animals and plants use anti-oxidants. Plants make vitamin E, a fat-soluble compound which they store in seeds. There is a mass of evidence that vitamin E deficiency has a profound effect on the stability of essential fatty acids. In fact, vitamin E has been advocated as a vitamin supplement in old age in humans. Ascorbic acid (vitamin C) is required in large amounts in the human diet to help the formation of collagen and other intercellular materials, the development of cartilage, bone and teeth, and to assist the healing of wounds, and it is now known that it too stabilises essential fatty acids.

The anti-oxidant, butylated hydroxytoluene, is widely used in human foods to protect the polyunsaturated lipids against oxidation and in fact low concentrations of this compound in the diet of mice have been found to lengthen their lifespan by 30 per cent, presumably by protecting cell constituents (phospholipids) and delaying age changes.

If aspirin inhibits the synthesis of prostaglandins and so protects cell membranes, it too might prolong the lifespan of mammals. There is evidence that symptoms of some diseases are mediated by excessive production of prostaglandins and here again aspirin could well be effective. Prostaglandins probably play a role in the aetiology of spontaneous abortion and inhibitors of prostaglandin

synthesis might be beneficial in cases of threatened abortion.

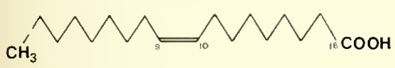
Perhaps, as a result of all these studies, it can be said that aspirin favours a shift from pro-inflammatory prostaglandins to less active agents, but does this help with the evaluation of the mechanism of action of aspirin?

Those who oppose the hypothesis that aspirin exerts its effects by inhibiting prostaglandin synthesis offer alternatives which also do not adequately explain all of its clinical anti-inflammatory action. Mechanisms based on stimulation of the anterior pituitary gland and the adrenal cortex, on uncoupling oxidative phosporylation reactions, and on stabilising lysosomal membranes are just three which have been considered.

Perhaps one for more serious comment involves the displacement from their binding sites in blood of certain amino-acids (such as tryptophan) or dipeptides such as phenylalanyl-phenylalamine) so that the free forms of these can then protect susceptible tissues from the effects of acute inflammatory stimuli. The necessity for continued administration in chronic diseases, coupled with the well-known observations that relapses often occur when treatment is stopped, also suggests that aspirin supports a natural defensive reaction in such cases.

This hypothesis therefore states that aspirin acts indirectly by increasing the proportion of free peptides in the blood, and time alone will decide whether or not this is more important in life than decreasing the production of prostaglandins.


Stearic acid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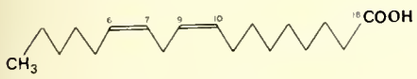
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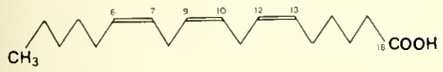
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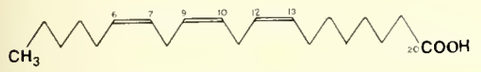
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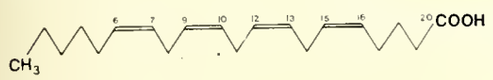
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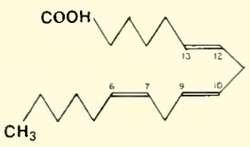
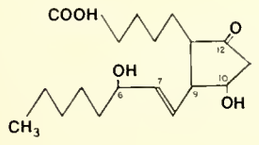
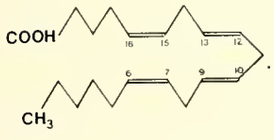
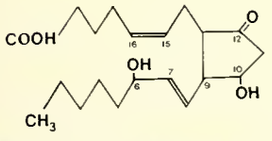

Homolinolenic acid


Prostaglandin E_1


Arachidonic acid


Prostaglandin E_2

Prostaglandin F series have —OH at C_{12}

The White Paper on NHS reorganisation

The integration of hospitals, general practice and community health services is the aim of the Government White Paper National Health Service Reorganisation: England. (HM Stationery Office, price £0·68.)

The Government claims the patient will benefit from a service which unites for the first time under one management hospitals, general practice and the community health services. Professional skills will work in teams and be concerned with the whole range of services at home, in the surgery, health centre or out-patient department or for the in-patient.

There will be a new network of local community health councils. Half the members will be appointed by the elected councillors of the district local authority. The other half will mainly be voluntary service representatives. There will also be a Health Service Ombudsman.

At national level there will be a reorganised Department of Health and Social Security responsible for central strategic planning and monitoring. At regional level there will be 14 new Regional Health Authorities responsible for general supervision and regional planning. At local level there will be about 90 new Area Health Authorities.

Plans for unification

The Government's plans for unification, states the White Paper, provide for a single administering body locally. This body, the Area Health Authority, will be able to take a wide, unbiased and constructive view of the priorities across the whole range of needs served by the family practitioners, the community health services and the hospitals.

The day-to-day running of services will be based on the health "district", which will form the natural community for the planning and delivery of comprehensive health care. It will be up to the new health authorities to work out their districts with the help of advice from the Central Department, but outside London there will be about 150 districts. Each will contain a district general hospital—or several hospitals together carrying out the function of such a hospital—and will usually have a population of between 200,000 and 500,000. Areas with substantial teaching facilities will be described as "teaching areas" and the Area Health Authorities which administer them will be called Area Health Authorities (Teaching).

The Area Health Authorities will integrate the planning of the family practitioner services with other parts of the NHS. But there will be no change in the status of the general medical and dental practitioners, ophthalmic medical practitioners, opticians and pharmacists as independent contractors. Executive Councils will disappear but each Area Health Authority will set up a Family Practitioner Committee, which will be responsible for arranging contracts with individual practitioners, administering their remuneration and terms of service and the existing statutory disciplinary arrangements. The composition of the Committees will be similar to that of Executive Councils at present. There will be 30 members, half appointed by the professions.

Special arrangements are necessary for London to take account of the structure of its health and related services.

The Regional Health Authorities will have far wider responsibilities than the old Regional Hospital Boards, because they will cover what are now family practitioner and community health services as well as hospitals, and will co-ordinate medical and dental teaching. There will be the same number of Regional Health Authorities—14—but regional boundaries will be adjusted to conform with the new health area boundaries. Regional Health Authorities will be accountable to the Secretary of State both for their own activities and those of Area Health Authorities.

The Central Department will be responsible for overall budgeting and accounting for health expenditure.

The Government believes that regional and area authorities should be composed of part-time members. Members will be unpaid, but powers will be sought to pay chairmen on a part-time basis.

The Secretary of State will appoint both chairmen and members of Regional Health Authorities, after consultations with interested organisations, and will also appoint the Chairmen of Area Health Authorities after consultation with the Chairman of the Regional Health Authority. Four members will be appointed by the corresponding local authority and one nominated by the university. In areas with substantial teaching facilities the university will nominate two. The rest will be chosen and appointed by the Regional Health Authority, after consultation with organisations, including the main health professions. The proportion of professional members will not be prescribed, but an Area Health Authority will always include doctors and at least one nurse or midwife

Professional advisory machinery

Strong profesional advisory machinery will be built into the new structure. It will function at each level of management "and will ensure that the health professions exercise an effective voice at all levels in the planning and operation of the NHS".

The details will be worked out in consultation with the various professions in readiness for 1974. Though the detailed arrangements will vary according to the circumstances of the individual professions, the White Paper states it is clear that:

(*a*) at least the following professions must be covered: doctors, dentists, opticians, pharmacists, nurses and midwives:

(*b*) the arrangements must include provision for successors to the local medical, dental, optical and pharmaceutical committees, since they will, as now, have important statutory and other functions to perform, eg the appointment of members to the Family Practitioner Committees;

(*c*) the arrangements should also carry into the reorganised service the best of the experience already gained in the existing service (e.g. the developing "Cogwheel" structure, other satisfactory arrangements at Hospital Management Committee and individual hospital level, and the advisory systems on professional matters built up by the Regional Hospital Boards); and should take account of the interests of medical, dental and nursing education.

Advisory bodies

At the national level, the Department of Health and Social Security must have available to it expert opinion on a wide range of matters, many of which are highly technical, relating to the provision of the National Health Service. Advisory bodies will continue to be the main source of this advice. They are either set up as standing bodies or appointed as required.

The main standing advisory body for the Department is the Central Health Services Council. The White Paper proposes new appointments to the Council to advise from the patient's viewpoint.

There will be one of the new community health councils in each district to give local people an effective voice in the running of the new health service. Half its members will be appointed by the local government district councils, and the rest mainly on the nomination of voluntary bodies. The White Paper envisages a total membership of between 20 and 30.

At present, statutory responsibility for administering the NHS is divided between the Secretary of State for the hospital services, the executive councils for the family practitioner services and local authorities for the other community personal health services. In future an overall responsibility will rest on the Secretary of State and there will be a clear line of responsibility for the whole NHS from him to the Regional Health Authorities and through them to the Area Health Authorities. But the authority doing the job will be left to get on with it with a minimum of interference.

As already announced, the Government has decided to establish a Health Service Ombudsman to investigate complaints against authorities. Legislation necessary to establish the Commissioner will form part of the NHS Reorganisation Bill, but the Commissioner will be able to start work before the unified service comes into operation on April 1, 1974.

The new area and regional authorities will be appointed as soon as possible after the necessary legislation has been passed. They will therefore be in existance, in "shadow" form, for some months before they take over responsibility.

Meantime joint liaison committees in each region and area will deal with as much of the preparatory work as possible. They have a special responsibility for ensuring that NHS staff are fully consulted and informed.

COMMENT

More problems ahead

Pharmacists have now had sufficient experience of White Papers to approach them critically if not cynically. They realise that the transition from a general statement to a precise regulation can be achieved by a number of routes with only some of them ending at the original anticipated destination.

There are gaps still in the legislation emanating from the White Paper dealing with the control of medicines even after an interval of years. However, according to the White Paper the legislation concerning a unified NHS is being prepared and "will be introduced in time for the reorganised NHS to come into operation on the same date as the reorganisation of local government, on April 1, 1974". It may be stating the obvious to say that whether or not that date is achieved will depend on whether Parliament approves the new proposals, for it must not be overlooked that many aspects of the NHS are now almost political tenets that no opportunity will be missed to air views in the forthcoming debates.

Nevertheless pharmacists will need to be ready to ensure they are able to take advantage of the declared Government intention to build "strong professional machinery" in the new structure. "The details will be worked out in consultation with the various professions in readiness for 1974". The White Paper continues ". . . it is clear that . . . at least the following professions must be covered . . . doctors, dentists, opticians, pharmacists and nurses and midwives . . ."

A quick perusal of the White Paper gives the feeling that all the professions will need to exercise a continuous vigil to ensure that the "single unified structure" of a reorganised Department of Health and Social Security, 14 new Regional Health Authorities and 90 new Area Health Authorities with "a more systematic and comprehensive planning process than now exists" does not become an all-enveloping organisation striving for tidier management procedures and stifling the independent thought that has been an essential attribute in the progress of medicine and pharmacy.

Criticism justified

The new Voluntary Price Regulation Scheme announced by the Secretary of State for Health (see p 198) is again a compromise resulting from the tough negotiations that have been going on between the government department and the Association of the British Pharmaceutical Industry almost since the last scheme was agreed in 1969.

The new agreement is intended to last for five years—two years longer than the previous one—and that should give both the Department and the industry a breathing space in which to operate.

The annual report of the ABPI said members' experience of the operation proved "cumbersome and onerous"; cumbersome in that small companies had to apply for permission each time an increase was required, the level of sales to NHS for any branded product being set at £5,000 a year. This was surely an out of date figure more realistic of the 1930s than 1970s. The Secretary of State has acknowledged this and the limit is now £150,000 a year (or £50,000 where a product accounts for more than 10 per cent of the company's total sales to NHS).

Yet another relief for the smaller manufacturer is in Sir Keith's package. Companies with annual sales of up to £100,000 to the NHS will now be relieved of sending financial information to the Department and those with sales of from £100,000 to £750,000 will have to supply a much simpler return.

The Department had sought to "devise criteria of profitability and sales promotion, but the detailed financial returns received by them convinced the Department that "such wide variations in trading patterns and capital structure exist" in the industry that it could not devise such criteria. The industry had made a similar attempt and was similarly unsuccessful.

All in all the ABPI's criticism of the 1969 scheme has been seen to be justified.

Irish Pharmacy Congress secrets

A detailed programme of the Irish Pharmaceutical Congress which has the theme "Pharmacy in the E.E.C." is now available from the secretary, E. Kennelly of 6 Lower Castle Street, Tralee. However, Mr Tom Harty, Congress chairman says that they have decided to omit from the printed programme some special features "a surprise element we feel makes it worth holding back".

The Congress is being held at the Mount Brandon Hotel, Tralee October 8-11.

At the symposium on Monday M. Boris Brus, President of the Belgian Pharmaceutical Society will lecture on "Pharmacy in the E.E.C." There are further lectures on "The History of Pharmacy in Ireland" by Mr. Norman Cooper, and "The Pharmaceutical Aspects of Diabetes Mellitus" by Professor Denis J. O'Sullivan.

At the banquet on Wednesday the guest of honour will be Mr. Erskine Childers, T.D. Tanaiste and Minister for Health.

To back up the seminar—"A Review of the Operation of the Health Services for the Initial six Months" there is to be a special information desk at the Congress to enable pharmacists to discuss with representatives of the Department of Health any problems arising from the scheme.

The official opening of the Congress takes place at the Ashe Memorial Hall. On Sunday evening there is a "folk concert" followed by the "Congress Club".

The annual meeting of the Pharmaceutical Society of Ireland takes place on Monday, October 9 at 8·30pm. On Tuesday at 10.30 Mr Murty O'Connor, chief pharmacist Meath Hospital Dublin speaks on "drug interaction".

Sir Alan Wilson, chairman of Glaxo Holdings Ltd, presents the 1971 Glaxo travelling fellowship for Science Writers to Miss Angela Croome, editor of Spectrum. Three fellowships, which are awarded each year, are worth £500 and enable the winners to travel overseas for further study of their chosen subjects

LETTERS

Fire-retardant paints

Alan Guy's article (*C&D*, July 1, p 18) on fire-protection was, I am sure, of great interest to many of your readers, particularly set against the current background of relentless increases year after year of property lost or damaged by fire.

Mr Guy concentrates, quite rightly, on the methods of extinguishing a fire. However, on the "prevention rather than cure" principle, I would like to draw your readers' attention to one simple and inexpensive method by which the fire hazard of a commercial premises can be reduced considerably, namely by the use of fire retardant paints.

These paints work on one of two general principles. Either the paint simply will not burn and hence impedes the spread of flame, or in addition to not burning, the paint is designed to bubble and foam in the presence of a fire and forms a thick carbonaceous insulating layer which restricts the flame-spread and also insulates the sub-strata from the fire. These latter types of paint are called "intumescent".

The extra time gained by the use of these paints in that critical stage in the growth of a fire from small beginnings to uncontrollable blaze, can make the difference between minor inconvenience and complete ruin.

I should be pleased to supply further details about this method of fire protection including recent technical developments, manufacturers, etc.

B. K. Rogers
Monsanto Europe SA
Place Madou 1
B-1030 Brussels, Belgium

Nostalgia again

I am grateful to Mrs Corfield for her kind letter (*C&D*, June 24, p 869) and venture to assure her that the *complete* group did turn out in "The Square" in 1916. It was wartime, and classes were smaller. My proof is a photograph (not, alas, up to *C&D* reproduction standard) but it shows Miss Ella Caird, as she then was, and her husband-to-be, on the front row. Mr B. W. Melhuish was the brilliant dispenser in mind (*C&D*, June 3, p 782). Incidentally, I did try to master the violin some years later, but never reached anything like concert pitch.

May I congratulate you, Mr Editor, on giving so much of your precious space to the pleasant things of life, in happy contrast to the daily Press, radio and TV, which too often emphasise its more gruesome features.

E. H. Shields
Stalybridge, Ches

Unprofitable

I am writing to inform you of a recent experience I have had with Messrs Unicliff with regard to their price increase for slimming aids, as I feel there may be many other people who have been placed in this iniquitous position.

I placed an order with the representative of this firm on the 28th June, having discussed with him the netted down price of the various items in order to determine the appropriate selling prices. On checking the invoice received three weeks later, I found that a price increase had been put into effect—unbeknown to me—and I had been selling stock for approximately two weeks at virtually no profit.

I contacted the firm in question and was informed that there had been an increase in price on 3rd July but due to an error on their part no advance information had been circularised to this effect.

As a result of my protestations I was promised a credit note for the difference in the price I had discussed with the representative and the price I had been actually charged. I then enquired whether other chemists would receive similar treatment in view of the fact that there was no forewarning of an increase, and their representatives were quoting the old prices. I was informed that the matter was "under consideration".

May I suggest that any chemist who has had a recent order from Messrs Unicliff should check his selling prices in relation to the invoice price in order to ensure that he has been "favourably considered"!

David A. Charvonia
London E8

Plea from Sunderland

I have recently circulated a postal survey on the Chemists' NHS contract with Executive Councils to a sample of about 1,500 independent pharmacies in Great Britain.

I would be grateful if I could use your columns, both to encourage those principals who have received the questionnaire to support this inquiry by completing and returning their copy as soon as possible and to thank those who have already co-operated in this way.

I. F. Jones
School of Pharmacy, Sunderland Polytechnic
Sunderland SR 1 3SD

Pharmaceutical industry gets a simpler VPRS

Following an investigation into the fourth voluntary price regulation scheme (VPRS) which has been operated since November 1969, Sir Keith Joseph, Secretary of State for Health, told Parliament last week that he had agreed with the Association of the British Pharmaceutical Association to make a number of changes.

This, he said would be done while still "retaining the essential principle, that pharmaceutical companies should achieve a fair and reasonable level of profitability in relation to the capital employed on their home National Health Service business."

Although the 1969 scheme provided that the Department should try to devise criteria of profitability and sales promotion, the detailed financial returns which were received from all companies demonstrated such wide variations in trading patterns and capital structure that he concluded that it was impracticable to devise such criteria. Profitability of individual companies would therefore continue to be judged in the light of all the circumstances of the company and in any instance where it appeared to be excessive the Department would negotiate for price reductions. "Excessive sales promotion expenditure" must continue to be assessed according to the facts of the individual company, he said.

The industry made an important contribution to the economy through its rapidly increasing exports and through further investment in research and manufacturing capacity. "We have in the past taken account of factors of this kind but they are now written more formally into the amended scheme," said Sir Keith.

He admitted that the supply of financial information had been a burden on small companies whose profitability had generally proved not to be high enough to justify the Department opening negotiations with them. He had therefore decided to exempt companies with annual sales to the NHS not exceeding £100,000 a year from providing regular financial information; companies with sales from £100,000 to £750,000 would have to supply a much simplified return. The right to call for full financial returns from any company in either of these groups if circumstances appear to warrant it would be retained.

The 1969 VPRS had a price restraint provision whereby companies were required to justify to the Department intended increases in the price of any branded medicine with annual NHS sales of £5,000 or more.

Sir Keith admitted the control figure was set too low for practical purposes and in the amended Scheme advance justification of price increases would be required in respect of products with sales in excess of £150,000 a year or in excess of £50,000 a year where a product accounted for more than 10 per cent of a company's total sales to the NHS. These price restraint provisions applied to all companies.

The revised scheme is intended to operate for five years.

ABPI annual report

The ABPI's annual report 1971-72 published last week described the reaction of its members to the 1969 VPRS as "cumbersome and onerous" and basically inappropriate to the economic circumstances of 1971". In May that year ABPI prepared a document outlining their arguments and advocating "a radical simplification" of the scheme. Sir Keith's announcement last week is obviously the result of investigation motivated by that document.

RECENT DEVELOPMENTS IN ANTIBIOTICS

By Brian Lynn, BPharm, MPS, head of medical information and services, Beecham pharmaceutical division

It is not surprising that antibiotics are of abiding scientific interest. They provide the clinician with his main weapon in the treatment of infectious diseases. Their fascination to the pharmacognosist and chemist lies in their variety of sources and amazing diversity of structure; whilst their various antimicrobial spectra and modes of action and their often widely differing pharmacological behaviour are rich fields of study for the microbiologist and the pharmacologist.

Chemically, the antibiotics contain examples of aliphatic, aromatic, heterocyclic, carbohydrate and peptide units. Despite their diversity (and sometimes complexity) of structure, however, they apparently arise from variations on a limited number of biogenetic themes. This provides a basis for a rational classification in chemical terms (I).

Many antibiotics contain structures or major structural fragments which are derivable mainly from amino acids, from sugars, or from acetate or propionate units. Examples of the more important antibiotics which fall into these three groups are given in table I. The groups themselves may be subdivided into families, the members of which have closely related structures arising, with minor changes, from a common biosynthetic process.

TABLE I. Classification of antibiotics according to their possible biogenetic origins and chemical structure.

Antibiotics derivable from amino acids
FROM ONE AMINO ACID: D--cycloserine, chloramphenicol.
FROM TWO AMINO ACIDS: penicillins, cephalosporin C.
POLYPEPTIDES: actinomycins, bacitracins, polymyxins, viomycin.
Antibiotics derivable mainly or partly from acetate or propionate units
FUSED-RING SYSTEMS: fusidic acid, tetracyclines, griseofulvin.
MACROLIDES: erythromycin, oleandomycin, carbomycin, spiramycins.
POLYENES: amphotericins, nystatin.
Antibiotics derivable from sugars
AMINOGLYCOSIDES: streptomycin, neomycins, paromomycin, kanamycin, framycetin, gentamicins.

Proposals for a fairly detailed classification of antibiotics in purely chemical terms were recently put forward (2). The scheme was used by the authors to classify the large numbers of antibiotics of known structure obtained from actinomycetes.

Table II summarises the biological sources of the more widely used antibiotics.

TABLE II. Sources of major antibiotics

ACTINMYCETES: aminoglycosides, antitumour antibiotics (eg actinomycins, mitomycin C), chloramphenicol, D-cycloserine, lincomycin, macrolides, novobiocin, polyenes (antifungals), rifamycins, tetracyclines.
BACTERIA: bacitracins gramicidins, polymyxins.
FUNGI: cephalosporin C, fusidic acid, griseofulvin, penicillins.

Important developments in the antibiotic field have been made in recent years, and these have involved both agents of entirely natural origin and those obtained by chemical modification of naturally occurring substances. In discussing these advances, I shall confine myself to a consideration of those agents which have proved to be of clinical importance —their origin, chemical nature and, briefly, their properties and clinical applications.

Since screening for antibiotics, particularly of soil micro-organisms, has taken place on an enormous scale during the past thirty years, it is not surprising that the rate of discovery of clinically important agents has slowed down during the last decade. Nevertheless, several new antibiotics have been isolated, and three of these have already become widely used in clinical practice, namely fusidic acid, lincomycin and gentamicin.

Structural modification

Emphasis during the 1960s has been on structural modification of existing antibiotics, so as to provide compounds with new or enhanced properties. Outstanding success in this field has been achieved by the development of the semi-synthetic penicillins. Subsequently, semi-synthetic derivatives of cephalosporin C have been prepared, and three have so far been introduced into medicine. The latest group of antibiotics to be exploited in this way are the rifamycins.

A further interesting class of natural products, obtained from various species of Streptomyces, are the antitumour antibiotics. These are agents which interfere with nucleic acid synthesis, either in microorganisms or in mammalian cells. They are consequently too toxic for use as systemic antimicrobial drugs, but have been found to have cytostatic and antitumour activity. A number of these compounds have undergone human clinical trial and several, including actinomycin D and mitomycin C, now have a useful place in cancer chemotherapy.

BIOSYNTHETIC ANTIBIOTICS

Fusidic acid

The steroids are among the most versatile of all biologically active molecules, and considerable alterations in the nature of the activity possessed by members of this group may be brought about by comparatively minor changes in structure or orientation. However, only in recent years has the antimicrobial activity of certain steroid compounds been utilised.

The first microbiologically active steroid to be studied was helvolic acid, isolated in 1943 from a strain of *Aspergillus fumigatus* (3), though its steroid character was not realised at that time. Cephalosporin P_1, a similar substance with greater antibacterial activity, was isolated some eight years later (4). It has subsequently been shown that both compounds are steroids, closely related in structure to each other (5) and to fusidic acid.

Fusidic acid was isolated from the fermentation broth of *Fusidium coccineum* (6), a mould which was found growing on a deposit of stale monkey faeces in Japan —one of those delightfully bizarre features one comes across in the antibiotic field! Its structural formula is shown in figure 1, from which it can be seen to possess the basic cyclopentenophenanthrene ring system of steroids. The side-chain at C-17 bears a carboxyl group. The relative and absolute stereochemistry of fusidic acid has been established (7) and the stereochemical configuration of the ring system has been shown to differ from that normally found in tetracyclic triterpenes and steroids.

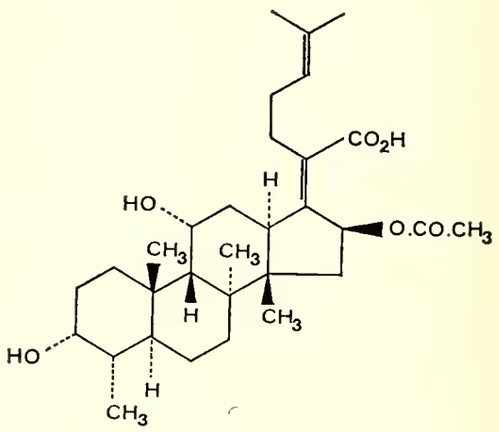


Figure 1. Structure of fusidic acid

Some structure-activity relationships of fusidic acid derivatives have been investigated (8). Fusidic acid itself is some 8-16 times more active against staphylococci than cephalosporin P_1 and helvolic acid, respectively, and this activity is maintained in 24, 25-dihydrofusidic acid. Other modi-

fications were, however, found to decrease activity.

Antibacterial properties. Fusidic acid is used clinically as the sodium salt, which is active against Gram-positive bacteria and the Gram-negative cocci (9, 10). Its most useful property is good activity against *Staphylicoccus aureus,* and the compound is in fact used almost exclusively as an antistaphylococcal agent. It has a predominantly bactericidal effect (11), though large inocula of most cultures contain a small proportion of less sensitive cells (11-13); these may readily be selected out *in vitro,* and resistant strains may also emerge during therapy (11, 14). The mode of antibacterial action is probably by interference with protein synthesis.

Sodium fusidate is often used in conjunction with another agent, in order to prevent the emergence of resistance, and the antibacterial effect of such combinations has therefore been extensively studied. Synergy has been described with erythromycin or novobiocin (15), and with benzylpenicillin against staphylococci which produce small amounts of penicillinase (9, 10, 13). The majority of cells in the population are inhibited by sodium fusidate, while the small number of cells resistant to the latter are too few to bring about any significant destruction of penicillin and are killed by it (10, 16). This is not a true synergistic effect, as the two agents are acting on different parts of the bacterial population. It has been reported that sodium fusidate may be antagonistic *in vitro* (at least in certain concentration ratios) to the bactericidal action of penicillinase-stable penicillins, such as methicillin and cloxacillin, and to that of benzylpenicillin against penicillin-sensitive staphylococci (17), but it is doubtful whether this antagonism operates *in vivo* (18).

Pharmacology and toxicology. Sodium fusidate is well absorbed after oral administration (9, 11) and is usually used by this route, though an intravenous preparation is also available. Accumulation occurs on repeated dosage (9, 19). About 97 per cent of the absorbed material is reversibly bound to plasma protein.

The antibiotic is distributed into most tissues and body fluids (9, 19), and good levels have been reported in bone (20). It is largely metabolised in the body, and very little active drug appears in the urine (9, 11, 19).

Sodium fusidate is of low toxicity in animals (9, 19), and has been found to be non-toxic in clinical usage (19). Apart from occasional mild gastrointestinal disturbances and rashes it is well tolerated orally. Undesirable metabolic or pharmacological effects attributable to its steroid structure do not occur (21), and its protein catabolic effect is less marked than that of tetracycline (22).

Clinical usage. This antibiotic has proved to be a useful addition to the antistaphylococcal armoury. It has given good results, both alone and in combination, in a variety of staphylococcal infections, including severe conditions. Drug-resistant mutants have not usually been a clinical problem, but despite this some authorities advocate that to preserve its value sodium fusidate should always be used in combination with a second antibiotic.

Lincomycin

Lincomycin was isolated from the previously undescribed *Streptomyces lincolnensis,* var. lincolnensis, grown from a soil sample obtained from Lincoln, Nebraska (23, 24). Paper chromatography indicated that it differed from other major antibiotics. It is now known that lincomycin is related to celesticetin, and its chemical structure is shown in figure 2. It is composed of an amino acid, *trans*-L-4-n-propylhygric acid, in amide linkage with an 8-carbon amino sugar bearing a thio-alkyl glycoside group, methyl α-thiolincosaminide (25).

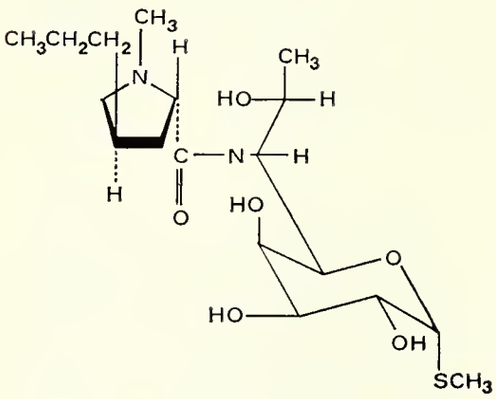


Figure 2. Structure of lincomycin

Lincomycin is used medicinally as the hydrochloride, which is very soluble in water. Chlorination results in replacement of the hydroxyl group at C-7 by a chlorine atom, with inversion (26). This synthetic modification, 7-chloro-7-deoxylincomycin hydrochloride, given the approved name clindamycin, has subsequently been introduced into medicine. It is both more active and better absorbed from the gastrointestinal tract than lincomycin itself.

Antibacterial properties. Although chemically quite different from the macrocyclic lactone structure with attached sugars which is possessed by erythromycin and its relatives (the macrolides), lincomycin closely resembles erythromycin in its antibacterial spectrum of activity (27, 28). Both agents are primarily active against Gram-positive bacteria, though lincomycin is usually less active than erythromycin against *Staphylococcus aureus, Streptococcus pyogenes, Streptococcus viridans, Streptococcus pneumoniae* and *Streptococcus faecalis.* Erythromycin, unlike lincomycin, also has useful activity against some strains of *Haemophilus influenzae* and *Neisseria,* and against *Mycoplasma pneumoniae.* Clindamycin is more active than lincomycin against staphylococci, pneumococci, haemolytic streptococci and enterococci (29), and against Bacteroides species (30).

Lincomycin also resembles erythromycin in its mode of action, which is by inhibition of protein synthesis and is apparently brought about by a similar mechanism (31, 32). Both are primarily bacteriostatic agents, but may show some bactericidal effect at higher concentrations. Lincomycin resistance in *Staph aureus* may be induced relatively easily *in vitro,* especially in erythromycin-resistant strains, and may also emerge during the course of treatment (28, 33, 34). There is partial cross-resistance between macrolides and lincomycin. Lincomycin-resistant variants of *Strep pyogenes* are commonly resistant to erythromycin, though the resistance may be unstable (35).

Pharmacology and toxicology. Lincomycin may be administered orally, intramuscularly or intravenously (36-38). Parenterally it is tolerated better than erythromycin. Urinary recovery of active drug is relatively low. Oral doses should be taken between meals, since absorption is significantly decreased by the presence of food (39). Clindamycin gives higher peak serum levels than lincomycin (29, 40, 41) and is consequently used at lower dosage: its absorption is also affected to a lesser extend by food. Lincomycin is well distributed into most tissues (37, 38), including bone (41, 42).

Lincomycin appears to be a non-toxic compound. It does, however, cause diarrhoea (or other gastro-intestinal disturbances) in a rather high proportion of patients (43). Though clinical evidence with clindamycin is as yet relatively limited, it may well produce a lower incidence of this side effect, since it is used at lower dosage and is more efficiently absorbed. Occasional hypersensitivity reactions to lincomycin have occurred.

Clinical usage. Lincomycin has given very satisfactory results in a range of Gram-positive infections, including acute and chronic staphylococcal osteomyelitis (44). The treatment of Bacteroides infections provides an additional promising application for lincomycin and clindamycin (45).

The indications for lincomycin or clindamycin broadly resemble those for erythromycin, particularly as regards their suitability for penicillin-sensitive patients. In addition, along with erythromycin and fusidic acid, they are among the agents available for use, in pairs, in the treatment of infections due to methicillin-resistant staphylococci. Because of the possibility of resistance developing, it has been suggested that in staphylococcal infections it is advisable for lincomycin always to be used in conjunction with another agent. There are, however, what would seem to be valid reasons for believing that lincomycin and its near relative should not be used concurrently with chloramphenicol or one of the macrolides, since there may be mutual antagonism in binding to the 50S subunit of the ribosome (46).

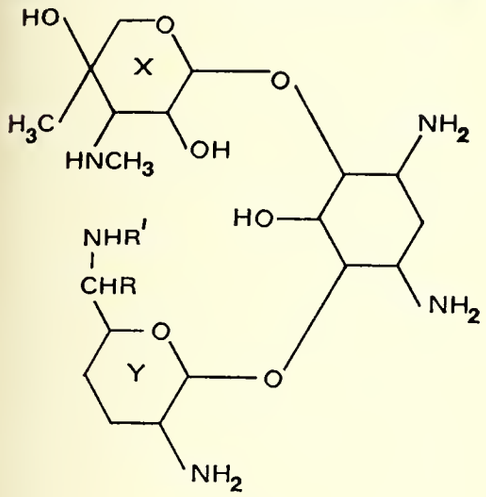
If its *in vitro* advantages are borne out in clinical practice, it is likely that clindamycin will gradually replace lincomycin, particularly if a parenteral form becomes available.

Gentamicin

During studies of a large series of Micromonospora isolates, two previously undescribed species, *purpurea* and *echinospora,* were found to produce a new broad-spectrum antibotic complex, which was named gentamicin (47-49). It is so far the only clinically available antibiotic

obtained from this genus. Gentamicin is a basic, water-soluble, stable substance which, together with streptomycin, neomycin, framycetin, kanamycin and paromomycin, belongs to the aminoglycoside family. It is used in medicine as the sulphate.

The available form of gentamicin is a mixture of three closely related components, referred to as C_1, C_{1A}, and C_2, the structures of which are summarised in figure 3. They consist of two different



gentamicin C_1, $R=R'=CH_3$

gentamicin C_{1A}, $R=R'=H$

gentamicin C_2, $R=CH_3$, $R'=H$

Figure 3. Structures of the three components of the gentamicin complex

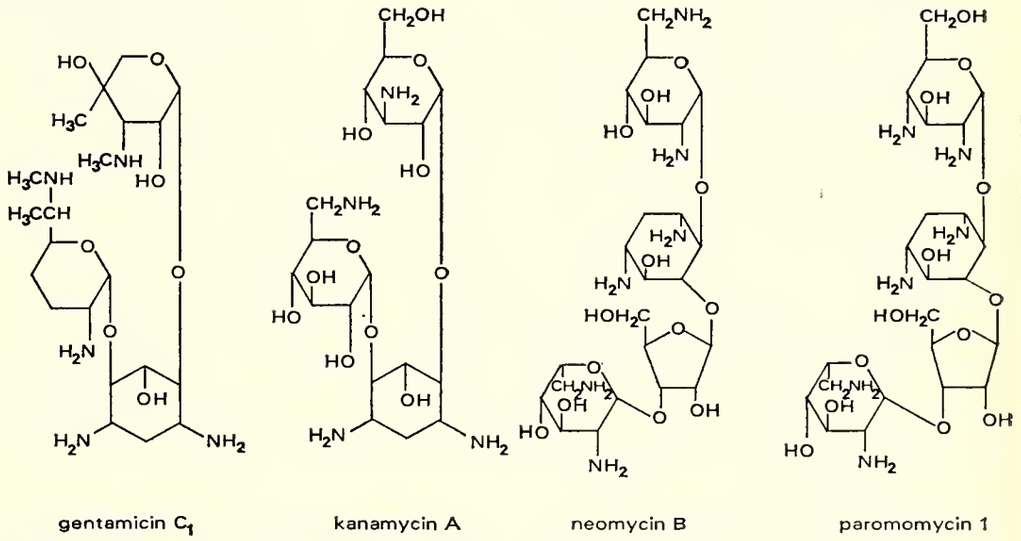
amino sugars in glycoside linkage with 2-deoxystreptamine (50). Deoxystreptamine is common to several other aminoglycoside antibiotics, including neomycin, kanamycin and paromomycin. In gentamicin it is attached to two novel compounds, a methylamino sugar (X) which has been given the name "garosamine", and a 2, 3, 4, 6-tetradeoxy-amino sugar (Y) which has been named "purpurosamine". The absence of hydroxyl groups in the latter is an unusual feature, which may have biological significance, in that the 3-hydroxy position of the methylamino sugar in aminoglycoside antibiotics is the specific site of phosphorylation or acetylation by inactivating enzymes.

The three gentamicin components differ in the presence or absence of methyl groups at positions R and R^1 (figure 3). The structural relationship between the fully methylated component, gentamicin C_1, and other 2-deoxystreptamine-containing aminoglycosides is illustrated in figure 4. Both neomycin and paromomycin have three additional amino sugars, while gentamicin and kanamycin have only two.

Antibacterial properties. The aminoglycosides are active against Gram-negative bacilli, including *Escherichia coli*, Klebsiella, Enterobacter (Aerobacter) and Proteus species, and also against *Staphylococcus aureus;* but not against other Gram-positive cocci, except in relatively high concentrations. Broadly speaking, gentamicin has greater activity against most species than the other members of the group, and has the additional valuable property of good activity against *Pseudomonas aeruginosa* (*pyocyanea*) (47, 51-54). Though occasional strains of this organism may respond to other antibiotics, the main treatment available previously for Pseudomonas infections was with polymyxin B and polymyxin E (colistin), but clinical results were variable.

The aminoglycoside antibiotics are rapidly bactericidal, though their mode of action is complex: it primarily involves interference with protein synthesis, apparently by attachment to the ribosome, causing misreading of messenger-RNA (53). Single-step mutants showing a high degree of resistance to streptomycin may emerge fairly quickly. Acquired resistance to other members of the group emerges much more slowly, but may occasionally appear during therapy. There is a degree of cross-resistance between the various aminoglycosides, but this is by no means complete (47, 51-54). Gentamicin, like the other aminoglycosides, is more active at slightly alkaline pH than at acid pH, but the effect is less marked than with streptomycin (52, 53).

Pharmacology and toxicology. Very little gentamicin is absorbed from the alimentary tract and it is administered by the intramuscular or intravenous routes. Intramuscularly, the peak serum concentration is reached in half to one hour, and significant levels persist for 6-8 hours (55, 56). It is largely excreted in unchanged form by the kidneys, almost entirely by glomerular filtration (55, 56). The adult dosage now usually recommended for systemic infections in patients with normal renal function is 80 mg three times a day for 7-10 days (56), which is double that initially employed, but still lower than that of streptomycin or kanamycin.



gentamicin C_1 kanamycin A neomycin B paromomycin 1

Figure 4. Antibiotics containing 2-deoxystreptamine

Dose for dose, gentamicin is more ototoxic than either streptomycin or kanamycin. The risk of damage to the eighth nerve, particularly the vestibular branch, is greatest in patients with renal impairment, in whom higher serum concentrations would be obtained (54). Labyrinthine damage occurs with serum levels exceeding 10 μg/ml: levels should therefore be measured during treatment of patients with impaired kidney function, so that the dosage frequency can be reduced accordingly. Renal toxicity is infrequent at normal therapeutic dosage (54).

Clinical usage. Though serious infections due to *Pseudomonas aeruginosa* used to be relatively infrequent, they have become more prevalent in hospitals in recent years as those caused by other bacteria (particularly staphylococci) have been more effectively controlled. The ability of the organism to survive in disinfectant solutions has played an important part in its spread (57). Pseudomonas infections occur particularly in patients with low resistance —including infants and old people, those with chronic or debilitating conditions such as leukaemia, severe burns and certain chronic diseases of the chest and urinary tract, those who have undergone surgery, and those having radiation therapy or long-term treatment with drugs which suppress the natural defences of the body. The prognosis in such patients is unfavourable, but it has certainly been improved by the advent of gentamicin and carbenicillin, a semi-synthetic penicillin which will be mentioned again later. In such patients the overall results with gentamicin, either alone or in combination with another agent, must be regarded as extremely satisfactory (53, 54). It is a particularly useful drug for the treatment of Gram-negative bacteraemia, because of its activity against the majority of Gram-negative bacilli.

A synergistic effect occurs between gentamicin and carbenicillin against many strains of *Pseudomonas aeruginosa* (53), and some workers consider this combination to be the treatment of choice for serious infections caused by this organism. Slow inactivation of gentamicin by carbenicillin has been demonstrated *in vivo* (58); but this is unlikely to be of clinical significance, except perhaps in patients with renal impairment, in whom excretion would be delayed and the agents consequently in more prolonged contact (58, 59). Interaction is, however, more marked in the syringe (60) or the infusion bottle (59) and mixing before administration should be avoided.

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References

1. Abraham, E. P., and Newton, G. G. F., *Brit med Bull*, 1960, 16, 3-10.
2. Sensi, P., and Coronelli, C., *I.C.I.A. Information Bulletin*, December 1971, no 9, 2-18.
3. Chain, E., et al, *Brit J exp Path*, 1943, 24, 108-119.
4. Burton, H. S., and Abraham, E. P., *Biochem J*, 1951, 50, 168-174.
5. Abraham, E. P., Biochemistry of some peptide and steroid antibiotics, John Wiley and Sons Inc, New York, 1957.
6. Godtfredsen, W. O., et al, *Nature (Lond)*, 1962, 193, 987.
7. Godtfredsen, W. O., et al, *Tetrahedron*, 1965, 21, 3505-3530.
8. Godtfredsen, W. O., et al, Antimicrobial Agents and Chemotherapy—(1965), American Society for Microbiology, 1966, 132-137.
9. Godtfredsen, W. O., et al, *Lancet*, 1962, 1, 928-931.
10. Barber, Mary, and Waterworth, Pamela M., *Lancet*, 1962, 1, 931-932.
11. Newman, R. L., et al, *Brit med J*, 1962, 2, 1645-1647.
12. Hilson, G. R. F., *Lancet*, 1962, 1, 932-933.
13. McDonald, Frances, *Med J Aust*, 1965, 1, 969-971.
14. Wright, G. L. T., and Harper, J., *Lancet*, 1970, 1, 9-14.
15. Jensen, K. A., and Kiaer, I., *Acta path microbiol scand*, 1964, 60, 271-284.
16. Waterworth, Pamela M., *Clin Med*, 1963, 70, 941-953.
17. Barber, Mary, *Proc roy Soc Med*, 1965, 58, 990-995.
18. Jensen, K., and Lassen, H. C. A., *Quart J Med*, 1969, new series *XXXVIII*, 91-106.
19. Stewart, G. T., *Pharmakotherapia*, 1964, II, 137-148.
20. Hierholzer, G., et al, *Arzneimittel-Forsch*, 1966, 16, 1549-1552.
21. Wynn, V., *Brit med J*, 1965, 1, 1400-1404.
22. Edwards, O. M., et al, *Brit med J*, 1970, 1, 26-27.
23. Mason, D. J., et al, Antimicrobial Agents and Chemotherapy—(1962), American Society for Microbiology, 1963, 554-559.
24. Herr, R. R., and Bergy, M. E., *ibid*, 560-564.
25. Hoeksema, H., et al, *J Amer chem Soc*, 1964, 86, 4223-4224.
26. Magerlein, B. J., et al, Antimicrobial Agents and Chemotherapy—(1966), American Society for Microbiology, 1967, 727-736.
27. Lewis, C., et al, Antimicrobial Agents and Chemotherapy—(1962), American Society for Microbiology, 1963, 570-582.
28. Barber, Mary, and Waterworth, Pamela M., *Brit med J*, 1964, 2, 603-606.
29. McGehee, R. F., et al, *Amer J med Sci*, 1968, 256, 279-292.
30. Ingham, H. R., et al, *J clin Path*, 1968, 21, 432-436.
31. Chang, F. N., and Weisblum, B., *Biochemistry*, 1967, 6, 836-843.
32. Wilhelm, J. M., et al, Antimicrobial Agents and Chemotherapy—(1967), American Society for Microbiology, 1968, 236-250.
33. Duncan, I. B. R., *ibid*, 723-729.
34. McGehee, R. F., Antimicrobial Agents and Chemotherapy—(1968), American Society for Microbiology, 1969, 392-397.
35. Lowbury, E. J. L., and Kidson, A., *Brit med J*, 1968, 2, 490-491.
36. Vavra, J. J., et al, Antimicrobial Agents and Chemotherapy—(1963), American Society for Microbiology, 1964, 176-182.
37. Ma, Pearl, et al, *ibid*, 183-188.
38. Medina, A., et al, *ibid*, 189-196.
39. McCall, C. E., et al, *Amer J med Sci*, 1967, 254, 144-155.
40. Phillips, I., *J clin Path*, 1971, 24, 410-418.
41. Holloway, W. J., Progress in Antimicrobial and Anticancer Chemotherapy, Proc. 6th Internat Congr Chemother, Tokyo 1969, Univ of Tokyo Press, 1970, 1, 687-692.
42. Holloway, W. J., et al, Antimicrobial Agents and Chemotherapy—(1963), American Society for Microbiology, 1964, 200-203.
43. Price, D. J. E., et al, *Brit med J*, 1968, 3, 407-409.
44. Holloway, W. J., and Scott, E. G., *Amer J med Sci*, 1965, 249, 691-695.
45. Tracy, O., et al, *Brit med J*, 1972, 1, 280-282.
46. Weisblum, B., *Lancet*, 1967, 1, 843-844.
47. Weinstein, M. J., et al, Antimicrobial Agents and Chemotherapy—(1963), American Society for Microbiology, 1964, 1-7.
48. Rosselet, J. P., et al, *ibid*, 14-16.
49. Luedemann, G. M., and Brodsky, B. C., *ibid*, 116-124.
50. Cooper, D. J., et al, *J infect Dis*, 1969, 119, 342-344.
51. White, A., Antimicrobial Agents and Chemotherapy—(1963), American Society for Microbiology, 1964, 17-19.
52. Barber, Mary, and Waterworth, Pamela M., *Brit med J*, 1966, 1, 203-205.
53. International Symposium on Gentamicin, *J infect Dis, April-May* 1969, 119, no 4 and 5.
54. Cox, Clair E., *Med Clin N Amer*, 1970, 54, 1305-1315.
55. Black, J., et al, Antimicrobial Agents and Chemotherapy—(1963), American Society for Microbiology, 1964, 138-147.
56. Gingell, J. C., and Waterworth, Pamela M., *Brit med J*, 1968, 2, 19-22.
57. Leading Article, *Lancet*, 1972, 1, 26-27.
58. McLaughlin, J. E., and Reeves, D. S., *Lancet*, 1971, 1, 261-264.
59. Noone, P., and Pattison, J. R., *Lancet*, 1971, 2, 575-578.
60. Lynn, B., and Jones, A., *Proc VIIth Internat Congr Chemother*, Prague, August 1971 (in press).

To be concluded

A name restored to the Register

A chemist whose name was removed from the Register for a year following a conviction for obtaining drugs for himself on a false prescription, was told at a meeting of the Pharmaceutical Society's Statutory Committee on July 26 that he could now return to pharmacy.

The Committee postponed judgment for 12 months on Mr Robert James Philip Billinge, Woodcote Way, Caversham, Reading, who appeared before the Committee as a result of being sentenced to nine months imprisonment at Aylesbury Quarter Sessions last December for stealing shop takings totalling £1,129·32 from R. Weston (Chemists) Ltd.

Mr St. John Howe, said that since Mr Billinge came out of prison in June he had been working in the pharmacy at Wexham Park Hospital, Slough.

Mr Billinge, told the Committee that the position he found himself in was due to his own foolishness. "I am interested in cars and I am afraid the money went that way," he said.

He wanted to do all he could to make restitution of the money as soon as possible, but if his name was removed from the register he did not know how he would be able to get the money.

Postponing judgment the chairman said he found it a most distressing case.

The Committee also postponed judgment for 12 months on Mr Richard Morgan, Medical Hall, Clynderwen, who owned a pharmacy at Market Square, Narbeth. He appeared before the Committee following a conviction on March 2 for allowing a cough linctus containing poison to be sold at his Clynderwen premises when a qualified person was not in charge.

Giving the decision the chairman said although no member of the public had suffered any injury as a result of Mr Morgan's misconduct it amounted to a very serious matter.

Four cases

The Committee dealt with the cases of four other pharmacists convicted by civil courts for permitting the sales of medicines containing poisons without qualified supervision.

One was warned he was in danger of being struck off if he failed to give an explanation of his conduct at the next sitting of the Committee, one was severely reprimanded and another was admonished and cautioned.

In the fourth case the Committee administered a caution to Mr Alfred Corris, 28 Bucks Road, Douglas, the secretary of the Isle of Man Pharmaceutical Association.

It heard that on the day his "summer season" pharmacy was due to close for the year, a Society inspector bought two medicines when no qualified pharmacist was present.

Mr Corris admitted that as a result of the sale on September 29 last year of a bottle of cough mixture and a packet of pain-killing tablets from the Palace Pharmacy, Central Parade, Douglas, he was convicted at Douglas Petty Sessional Court.

Mr Corris told the committee that at the time he thought his daughter, also a pharmacist, was at the shop. In fact his daughter had received a telephone call from his wife, who had just come out of hospital, and she had gone to collect her.

Mr Corris said that September 29 was to have been the last day that the shop would have been opened for that season. In fact dispensing at the pharmacy had ceased 10 days before.

Following his conviction he had offered his resignation as secretary of the Isle of Man Association—but it had been refused. The Committee Chairman, Sir Gordon Willmer, said they felt that perhaps Mr Corris was the victim of a certain amount of misfortune.

Last afternoon

"He happened to be caught in breach of his obligations on the very last afternoon of the summer season after which the premises where the sales took place would have been closed down. . . The fact that it was possible for these unauthorised sales to take place is no doubt due to a chain of most unfortunate circumstances . . . It is of course impossible for this committee to overlook these offences entirely but we have come to the conclusion that our responsibility as a Committee would be discharged if we administered a caution to Mr Corris against any repetition of such conduct in the future. But subject to that we propose to take no further action."

Mr Bernard Holding, Halton Road, Great Sankey, did not appear and was not represented when the Committee inquired into his conviction for allowing medicines containing poisons to be sold in his shop in Station Road, Great Sankey, without his supervision, and failing to label the medicines with a "poison" warning.

In a letter to the Committee asking for the inquiry to be held in his absence, Mr Holding said he had "a phobia regarding travelling any long distance." The letter went on: "If I could attend, my defence would be that my real crime is being a humanitarian."

Mr Peter St. John Howe, solicitor, said that in addition to his conviction on 14 charges under the Pharmacy and Poisons Act 1933 there was also a complaint against Mr Holding that he had been given several warnings by the Society since the offences about the need to observe the regulations. On one occasion in March last year an inspector of the Society visiting his shop found the key to the Dangerous Drugs cupboard in the lock of the cupboard door.

Adjourning the case until the next meeting of the committee, the Chairman warned Mr Holding that he was in danger of being struck off the register if he did not give them an explanation of his conduct.

The Committee severely reprimanded Mr Barry Elman, 11 Blackwood Avenue, Liverpool 25, who admitted a conviction at the Douglas Petty Sessions, Isle of Man, in December 1970, for allowing a poison to be sold without supervision.

Mr Howe said that, a police officer purchased travel sickness tablets from Greensills Chemists Ltd, Greensills Corner, Douglas, of which Mr Elman was superintendent pharmacist. At the time Mr Elman was in Liverpool and no pharmacist was in charge.

Mr Elman told the Committee he had been forced to leave the pharmacy due to his wife's illness. The staff knew they were not to sell any poisons without him there but they thought it was all right to sell to a policeman.

The Committee admonished and cautioned Mr Keith Lambert, of Westgate, Wakefield, who was convicted of illegal sales of medicines containing poison in March last year following test purchases by a Society inspector at his shop in Barnsley Road, Sandal, Wakefield. He was not present or represented when the Committee resumed their inquiry after a 12 month adjournment.

Mr Howe said it was a case of one man trying to run two pharmacies. Mr Lambert had now sold the shop in Barnsley Road and the inspector's report on the conduct of his business was satisfactory.

Announcing the Committee had decided Mr Lambert should be admonished and cautioned against such behaviour in future, the Chairman said they would also direct the secretary to write to him expressing their unfavourable view of his discourtesy in taking no steps either to appear himself or to be represented.

BOOKS

Glass and British Pharmacy 1600-1900. J. K. Crellin and J. R. Scott. *The Wellcome Institute of the History of Medicine,* 183, Euston Road, London, N.W.1. 9¼ × 6½in pp 72. £4·00.

This is more than just an illustrated catalogue based on the study of over 1,200 pieces in the collection created by Sir Henry Wellcome.

The authors begin by reviewing "commercial pharmacy" during the period under consideration. They look at the apothecaries' shop, window displays, specie jars and carboys and provide a succinct account that is likely to be quoted widely.

In the catalogue section there is a wide variety of glassware much of which is now the quarry of the collector.

The authors are to be congratulated upon the care with which they have gone about their work.

Whilst the student will of necessity find it advantageous to study the details, there are many who will enjoy perusing the pages with an increasing nostalgia in spite of the rather high price.

MARKET NEWS

Fresh round of price rises

London, August 2: After a relative lull, the pharmaceutical chemical industry appears to be in the process of another round of price rises. From August 1 mercurials were marked up for the second time within a month. Many of the barbiturates were also advanced on that date but phenobarbitone was not amongst them. One of the largest manufacturers of aspirin announced a 10 per cent increase in their schedules. Methyl salicylate was also increased and it is certain that other salicylate makers will follow the lead later this month. The new rates are given below.

Trading in crude drugs was almost at a standstill because of the strike of dockers. Price movements were attributed to lack of supplies. Those in an upward direction include Cape aloes, benzoin, cascara, chillies, gum acacia and pepper. Lower were Curaçao aloes, colocynth pulp and Costa Rican ipecacuanha. New-crop witchhazel leaves were on offer from origin at £820 metric ton.

Bois de rose, Chinese citronella and eucalyptus oil were dearer on the spot. Other essential oil prices were unchanged.

Pharmaceutical chemicals

Acetic acid: in 12-ton lots, delivered, per metric ton, BPC glacial £87·50; 90·5 per cent technical £81; 80 per cent grades pure £76·50; technical £69·50.
Acetomenaphthone: 100-kg lots £5·62½ kg.
Alcohol: (Per proof gal). Ethyl, fermentation in 2,500 bulk gal lots—SVR doubly rectified 96·1 per cent £0·303; absolute 99·9 per cent £0·315. In drums 900 gal minimum respective prices are £0·317, £0·329; Synthetic grades are 96 per cent, £0·233 and 99·9 per cent, £0·245 in tank wagon; £0·247 and £0·259 in drums for 900-bulk gal; industrial grade 95 per cent £0·164 in bulk and £0·178 in drums.
Amylobarbitons: 50-kg £3·75 kg; sodium £4·30.
Ascorbic acid: £2·36 kg; 5-kg £2·33 kg; sodium ascorbate plus £0·23; coated plus £0·10.
Aspirin: 10-metric ton lots £577·50 ton; 5-ton £583; 1-ton £594 [Increased rates see report above].
Atropine: (500-kg lots per kg) alkaloid and methonitrate £65·20; methylbromide £64·20; sulphate £52·90.
Barbitone: 50-kg lots £2·65 kg; sodium £2·65.
Benzoic acid: One-metric ton lots £30·42 kg.
Boric acid: BP grade per metric ton: granular £99; crystals £140; powder £110; extra-fine powder £114 in paper bags, carriage paid. Technical is £20 per 1,000 kg less than BP grades.
Butabarbital: 50-kg £5·35 kg; sodium £6.
Butobarbitone: £5·05 kg for 50-kg lots.
Calcium carbonate: BP precipitated £49 per 10,000 kg.
Calcium gluconate 250-kg lots £0·63 kg.
Calcium lactate: 250-kg £412 per metric ton.
Calcium pantothenate: £5·23 kg; 25-kg, £5·18 kg.
Calcium sodium lactate: metric ton. £709 for 50-kg lots.
Carotene: Suspension 20 per cent £16·73 kg.
Chloral hydrate: 50-kg lots £0·75 kg.
Chloroform: BP from £258 metric ton in 280-kg drums to £310 in 35-kg drums. 500-mil bottles £0·44 each.
Cinchocaine hydrochloride: £42·50 kg.
Citric acid: BP granular hydrous per metric ton 50-kg lots, £337; 250-kg £325; 1,000-kg £313. Anhydrous £358, £346, £334 respectively. Premium for powder £10.
Cocaine: Alkaloid £222 kg; hydrochloride £202·75. Subject to DDA Regulations.
Cyanocobalamin: up to 200-g lots £2 per g.
Cyclobarbitone: (50-kg) £4·15 kg; calcium £4·15.
Dextromethorphan: Hydrobromide £98·53 kg.
Digoxin: Up to 25-g lots £2·60 per g.
Dimidium bromide: 5-g lots £3·20 g.
Emetine: hydrochloride £375 kg;—bismuth iodide £212·50.
Ephedrine: (25-kg per kg) alkaloid £11·64; hyrdochloride £9·75; sulphate £9·50.
Ether: Anaesthetic BP— 2-litre bottles £0·87 each for under 350 litres; £0·81 for over 350 litres; 32-kg drums £0·41 kg for 500-kg lots. Solvent BP —per metric ton in drums from £294 for 500-kg lots in 16-kg drums down to £266 in 130-kg drums; 250-kg from £304 to £276.
Fentichlor: 50-kg lots £1·73 kg.
Folic acid: 5-kg lots £16 kg.
Gallic acid: 1,000-kg lots £1·62 kg.
Hydroxocobalamin: £5·25 per g.
Hyoscine hydrobromide: £314·25 kg.
Hyoscyamine sulphate: (100-g lots) £59 kg.
Ichthammol: 1,000-kg lots £0·52 kg.
Iodides: (Per kg) Potassium £2·16 (50-kg lots) £2·14 (250-kg); sodium £2·75 (50-kg).
Iodine: Chilean crude £2·08½ per kg; resublimed £2·87 in 50-kilo lots.
Iron ammonium sulphate: 100-kg £205 per metric ton.
Iron and ammonium citrate: (per metric ton) granules, 50-kg lots £650 1-ton £620. Scales 50-kg £820; 1-ton £790; green £830.
Iron phosphate: £470 for metric ton 50-kg lots.
Isoprenaline sulphate: 5-kg £16·50 kg.
Lactic acid: £570 metric ton for 50-kg lots.
Magnesium peroxide: 50-kg lots 23-25 per cent £0·59 kg.
Mercury salts: Per kg in 50-kg lots: ammoniated powder £4·45; oxides—yellow £5·20 and red £5·40, perchloride £3·70; subchloride £4·75; iodide £5·30 kg for 25-kg.
Mersalyl: Acid £15·75 per kg; sodium £21·50.
Methadone hydrochloride: Subject to DDA regulations £0·15 per g for 100-g lots.
Methyl salicylate: Per metric ton in 5-ton lots £467·50, 1-ton £473, 500-kg £478·50 [increased rates, see report above].
Methylated spirits: In 45-gal drums minimum 900 gal, delivered, industrial 66 op £0·308 per bulk gal; perfumery quality £0·359; mineralised 64 op, £0·322. In tank wagon, 2,500-gal, the rates are: £0·308, £0·359, and £0·30 respectively.
Narcotine: Alkaloid and hydrochloride in 25-kg lots £15 kg.
Nicotinamide: (Per kg) 1-kg £2·12; 25-kg £2·07 50-kg £2·02.
Nicotinic acid: (Per kg) 1 kg £1·93; 50-kg £1·83.
Oleic acid: BP is £206·70 per metric ton delivered.
Oxalic acid: 20-ton lots about £170 metric ton.
DPanthenol: £9 kg; 5-kg £8·50 kg.
Paracetamol: 1-metric ton lots £1·17 kg; 5-ton £1·14 kg. For direct compression £1·27 and £1·24 kg respectively.
Pentobarbitone: 50-kg lots £4·85 kg for acid and £5·15 for sodium.
Phemitone: 25-kg lots £4·24 kg.
Phenobarbitone: 50-kg lots £3·60 per kg; sodium £4·10.
Phenolphthalein: 250-kg lots £1 kg.
Pholcodine: 1-kg £198·36; 7-kg £189·20 kg; 60-kg £180.
Pyridoxine: £4·50 kg; 5-kg £4·47kg.
Pyrogallic acid: Pure 500-kg lots £4·73 kg.
Quinalbarbitone: Sodium and acid £5·35 kg for 25-kg lots.
Quinidine: Alkaloid (10-kg lots) £48 kg; sulphate (50-kg) £44.
Quinine: (Per kg in 85-kg lots) Alkaloid £29·25; bisulphate £22·85; dihydrochloride £28·60; hydrochloride £28; sulphate £24; hydrobromide (10-kg) £28·75.
Ribollavine: £13·35 kg; 5-kg lots £13·32 kg.
Saccharin: BP Powder 1 lb and over £0·85; soluble £0·77½ lb.
Salicylamide: (Per metric ton) 5-ton lots £700; 1-ton £710; ½ ton £720.
Salicylic acid: per metric ton 5-ton lots £405; 1-ton £425; 250-kg £470.
Sodium perborate: (Per 1,000 kg) **monohydrate** £283·50—**tetrahydrate** £145·75 kg.
Sorbitol: Powder £335 metric ton for over 250 kg.
Stilboestrol: BP in 25-kilo lots £33 kg.
Streptomycin: £11 kg base; dihydrostreptomycin £11·50 kg base.
Strycnnine: (kg) alkaloid £12·25; sulphate and hydrochloride £10·50.
Tannic acid: 500-kg fluffy £1·35 kg; powder £1·33.
Tartaric acid: (Per metric ton) 50-kg lots £437; 250-kg £432; £428 ton.
Terpineol: 50-kg lots £0·47 kg.
Theobromine: Alkaloid 100-kg lots £2·30 kg.
Theophylline: (50-kg) BP anhydrous, hydrate and ethylenediamine (aminophylline) £2·23 kg.
Thiamine: Hydrochloride and nitrate £7·55 kg; 5-kg £7·52 kg; 25-kg £7·50.
L-Thyroxine: £1·15 per g.
L-Triiodothyronine sodium: £2·50 per g.
Vitamin A: Oily 1 m iu per g £6·68 kg; 5 kg £6·58 kg; dried acetate 325,000 iu per g £3·48 kg; 500,000 iu, £4·55.
Vitamin D: Powder for tableting 850,000 iu per g, £17·81 kg; 5-kg £17·75 kg.
Vitamin E: (per kg) £7·15; 5-kg lots £7·05; 25 per cent dry powder £4·81 and £4·71 respectively; 50 per cent, £5·35 and £5·25.
Zinc carbonate: BPC 25-kg sacks £0·26 kg.
Zinc chloride: granular 96-98% £135 metric ton.
Zinc sulphate: heptahydrate £52 metric ton.

Crude drugs

Aconite: Spot £1,080 metric ton; £1,040 cif.
Agar: (lb) Kobe No 1 £0·85 cif; European £0·73.
Aloes: (metric ton) Cape primes £280 spot; £250 cif. Curaçao £775 spot; £725, cif.
Balsams: (lb) Canada: £2·05 spot; shipment £1·95 cif. **Copaiba:** BPC £1·25, Para £0·40. **Peru:** £1·10 £1, cif. **Tolu:** BP £0·70.
Belladonna: Leaves £300 metric ton spot, herb £250 and root £225. Shipment not offering.
Benzoin: BPC £0·80 kg spot; £0·70, cif.
Camphor: BP natural powder £0·85 kg spot; £0·80, cif. Synthetic BP £0·57 kg in 500-kg lots.
Cardamoms: (Per lb cif) Alleppy greens No 1, £0·85; prime seeds £0·90.
Cascara: Spot £440 metric ton; no cif offers.
Cassia: Lignea, whole £620 metric ton cif.
Chillies: Zanzibar £600 ton spot.
Colocynth pulp: Spot £730 metric ton.
Dandelion: Root £410 metric ton spot; £385, cif.
Ergot: Spot £3·10 kg.
Gentian: Root £400 metric ton spot; £390, cif.
Ginger: (ton) Cochin £240, cif. Jamaican No. 3 £1,050 spot; £840, cif. Nigerian split £210 spot, £192·50 cif; peeled £310 spot; £285, cif. Sierra Leone, no offers.
Gums: Acacia: Kordofan cleaned sorts £305 metric ton spot: £280 cif. **Karaya:** No. 2 faq £24 cwt spot. **Tragacanth:** (cwt) No. 1 spot £250, No. 2 £220.
Henbane: Niger spot £430 metric ton; £420, cif.
Honey: (ton) Australian light amber £263, medium £251. Canadian not available. Mexican £246. Chinese light amber £238.
Ipecacuanha: (per lb) Matto Grosso £2·50 spot; £2·40, cif, Costa Rican £2·20 spot; £2, cif.
Jalap: Mexican tubers £2 kg spot; £1·95, cif.
Kola nuts: West African halves £85 metric ton spot; shipment £78, cif.
Lanolin: Anhydrous BP minimum 1,000 kg £375 to £415; cosmetic grade £430.
Mace: Grenada £0·35 lb. fob.
Menthol: (kg) Chinese spot £6·30, shipment £6·30, cif. Brazilian spot £3·80, afloat £3·75, £3·70, cif, August-September.
Nutmeg: (Per ton, cif). Grenada: 80's £570; sound unassorted £490, defectives £375, all cif.
Nux vomica: Shipment £100 metric ton, cif.
Pepper: (ton) Sarawak black £385 spot; £342·50, cif; white £600; £495, cif.
Saffron: Mancha superior £82-kg.

Essential oils

Bois de rose: £3 kg spot; £2·75, cif.
Citronella: Ceylon spot £1·05 kg; £0·95, cif. Chinese £1·15 spot; £1·10, cif.
Eucalyptus: Chinese 80-85 per cent £0·72 kg in bond; shipment £0·68, cif.

COMING EVENTS

Advance information

Pakex 72—the International Packaging Exhibition. October 9-13. Olympia, London.

Courses and conferences

First International Conference on the Compaction and Consolidation of Particulate Matter. October 3-5. Hotel Metropole conference centre, Brighton. The conference will include a session on "pharmaceutical technology and applications". Registration forms from Powder Advisory Centre, 10 St John's Road, London NW11 0PG.